OFFICE IMMUNOLOGY

Including Allergy

THE GENERAL PRACTICE MANUALS

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(OTHER TITLES IN PREPARATION)

OFFICE IMMUNOLOGY

INCLUDING ALLERGY

A Guide for the Practitioner

Edited by

Marion B Sulzberger and Rudolf L Baer

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FOREWORD

OFFICE IMMUNOLOGY should fill a very real need The authors intend by their presentation of the most important immunologic methods to help the practicing physician in his use of technical procedures in the fields of allergy of immunization against infectious diseases etc In addition they include concise practicable information about allergic and infectious diseases

With this aim in mind the book was written not to bring new knowledge to the practicing physician but rather to assemble the necessary information under one cover Up to the present descriptions of the various procedures have been found scattered among many different books A handy report of the Committee on Therapeutic Procedures of the American Academy of Pediatrics discusses acute infectious diseases and biologicals but does not include the procedures in diagnosis and treatment of allergic diseases in childhood It is difficult to look up the pertinent facts when it entails examination of several pamphlets and textbooks

In the roster of authors of the present manual the combination of skilled dermatologists allergists and pediatricians is notable for many manifestations of allergy are seen not only by pediatricians and allergists but also by dermatologists Indeed many leading dermatologists like Bloch and Jadassohn in Europe not to mention their colleagues in the United States have made great contributions to allergy

I am convinced that the idea of the authors concerning the need for a book of this kind was correct and I hope the volume will meet with the success that it deserves

—BELA SCHICK

October 1946

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INTRODUCTION

IN THIS ERA of dramatic advances in chemotherapy some may be inclined to doubt the need of a text devoted to the physician's practice of immunology However we believe that one glance at the content of this book will show both the numerous and indispensable uses of immunologic methods and the continuing rapid progress in this field Even during this heyday of chemotherapy no trained physician can deny that the major progress in preventive medicine and public health has been accomplished through immunologic methods rather than through chemotherapeutic drugs Thus, many great scourges—smallpox diphtheria tetanus yellow fever—have virtually been mastered by immunologic prophylaxis and hygiene

Because the scope and the objectives of this text are both essentially new we have been unable to rely on precedent and thus have been faced with more than the usual difficulties in drawing the fine lines between proper exclusion and inclusion A short explanation of the manner of selection may therefore be in place here In selecting the immunologic procedures we have defined them as follows Those procedures which are based primarily on the remarkable property of living cells and living organisms to undergo a specific change on exposure to certain foreign agents—a change which confers on the exposed tissues the capacity to react differently on subsequent exposure to the same agents Thus procedures based on specific changes produced by toxins and by sensitizing agents are included regardless of whether free or circulating antibodies are demonstrable and regardless of whether the changes are attributable to immunologic substances produced by the patient himself (active immunization or hyposensitization) or are the result of supplying the patient with ready made immunologic substances

derived from others (passive immunization) *All such procedures* considered of actual or potential value to the practicing physician have been included

In determining what should come under the heading of office immunology we decided to include only those immunologic procedures which can be *performed on the patient himself* by the practicing physician *without* elaborate equipment or laboratory facilities and without removing from the patient any tissues or fluid for in vitro study Thus there have been excluded many eminently useful immunologic measures such as serologic tests for syphilis agglutinations other serologic and hematologic reactions and passive transfer tests for Prausnitz Kustner reagins

These arbitrary lines were drawn for two reasons first because it was felt that the practicing physician usually would not perform such tests himself but when necessary would either remove the material and send it to a laboratory for examination or refer the patient to a specialist second because a description of classic immunologic *laboratory* technics such as agglutinations and serologic tests for syphilis seemed unnecessary since they have been assembled and well described in numerous standard textbooks

The reader will note considerable variation in the length of the different expositions This was in part unavoidable in part deliberate The first two chapters on common technics purposely include many details because we believe that the physician will wish to study and to familiarize himself with the minutiae pertaining to the fundamental technics which he is called on to employ The sections on general infections are composed in a more clipped and telegraphic style for it is believed that the practicing physician familiar with the general principles and procedures will use these sections for reference rather than for study Independent of their relative clinical importance certain diseases have been discussed at much greater length than others Sometimes a longer discussion appeared necessary because the immunologic mechanisms and management of the particular disease might be less familiar to the

practitioner Sometimes the particular complexities and uncertainties or the fundamental importance of the problems required more detailed exposition. Among the diseases which seemed to require the fullest presentation were allergies" in the strictest sense namely eczematous contact type dermatitis the atopic diseases such as hay fever asthma atopic dermatitis urticaria and the allergic drug eruptions

The compilation of detailed specifications of the useful immunologic preparations procurable from pharmaceutical firms turned out to be an unusually difficult and delicate task. We felt, however that this book would lose much of its practical value if the full names of the supplying firms complete information regarding packaging and dosage schedules and other details of commercially available immunologic preparations were omitted. In compiling these details much time was spent in an effort to prevent mistakes and omissions The firms and products mentioned, and the information given have been obtained principally from *New and Nonofficial Remedies 1946* published by the American Medical Association and from the list of firms whose *therapeutic* biologic products have been tested and accepted by the National Institute of Health *(Public Health Reports* 60 1172 Oct 5 1945) Only in rare instances and then because of our personal conviction of the product s value has a preparation been included despite its exclusion from these lists In even fewer instances an officially listed product has been omitted because our own experience had convinced us that the material was without value

Despite all the care which has been exercised to be objective in specifying manufacturers and products and despite our requesting from all American manufacturers known to us the exact details regarding each product listed we are certain that errors will come to light Such errors are inevitable in describing products which are almost incessantly being introduced withdrawn or altered because of changing medical opinions and/or changing business practices All that we can do is to acknowledge the probability of inadvertent

errors and to state that if informed we shall make every effort to correct them at the first opportunity The advice of Dr M V Veldee and the assistance of Miss Sonia Tolins in the preparation of the manuscript are gratefully acknowledged

The reader will doubtless note much repetition in the various chapters and sections This too could not well be avoided without greatly impairing the practical usefulness of the book by increasing to a prohibitive degree the already necessarily large number of cross references

It is our hope that OFFICE IMMUNOLOGY may prove a useful text to the practicing physician We look forward to free and constructive criticisms which will suggest ways to improve any supplements or future editions of the text

Chapter One

COMMON TECHNICS

Diagnostic Procedures

Marion B Sulzberger W C Spain and Rudolf L Baer

THE FOLLOWING are the four important procedures commonly used in the endeavor to find eliciting agents in the many different forms of allergic disease

1 Evaluation of all pertinent clinical and laboratory findings
2 Pertinent history—both personal and familial
3 Appropriate skin tests
4 Effects of avoidance of and/or re exposure to suspected allergens

Many of the details of these four steps will be given in the discussions of the particular entities Only the common fundamentals of these approaches are presented at this point

STEP 1 EVALUATION OF CLINICAL AND LABORATORY FINDINGS

The first essential is that all available means be used to classify every case of allergic disease as precisely as possible If and when the condition is recognized as one commonly based on or associated with allergy every measure must be employed to ascertain the particular allergens or classes of allergens which first deserve consideration

Contact type eczematous dermatitis hives hay fever asthma drug reaction—indeed each form of allergic disease requires the consideration of different categories of allergens different approaches to the taking of history different management and often entirely different technics of skin testing Unless the physician will first study his cases by all clinical and laboratory means and thus make possible the selection of adequate and appropriate immunologic measures he will be doomed to failure just as surely as though he tried to diagnose tuberculosis by means of the Wassermann test or tonsillitis with a proctoscope

STEP 2 HISTORY

In many conditions an intelligent history can be taken only *after* the clinical and laboratory findings have been evaluated For example the clinical appearance distribution localization etc of cutaneous lesions indicate both the direction of the questioning and the allergens which are most suspect. In other conditions such as a clearcut case of hay fever or bronchial asthma the history may be taken first Obviously the historical facts of value will be different in a contact type eczematous dermatitis in a rhinitis in a presumptive drug eruption in a case of asthma or infantile eczema etc Furthermore the facts of value will differ in a contact type dermatitis of the hands and in one of the axillae or of the perioral areas in a pustular drug eruption and a fixed drug eruption in a rhinitis or asthma which is seasonal and one which is nonseasonal etc

Particulars of history taking are discussed in Chapters 5 and 6 and under the individual entities

STEPS 3 AND 4 SKIN TESTS AVOIDANCE AND RE EXPOSURE

After the clinical and laboratory findings have been weighed the case classified or diagnosed and the precise history taken the physician will generally find one of the following three situations (1) The data so conclusively implicate a certain allergen or certain allergens that further diagnostic procedures become superfluous

(2) Neither clinical and laboratory data nor the history brings to light allergenic exposures which are suspect Further clinical study questioning and detective work are required (3) Clinical data and history throw suspicion on certain allergens but the evidence is not conclusive In the last situation further evidence may be sought by means of skin tests and if necessary by observation of the effects of avoidance and/or exposure to suspected allergens

SKIN TESTS

GENERAL REMARKS

Immunologic skin tests have in common the object of discovering whether a skin site is more sensitive than normal (hypersensitive hyperergic) less sensitive than normal (hyposensitive hypoergic resistant or immune) or of normal sensitivity (normergic) to the particular agent applied This rule has only the rarest exceptions

No form of skin test can be expected to demonstrate whether the skin has *become* more sensitive (sensitized) or whether it has *become* less sensitive (hyposensitized desensitized or immunized) unless the results can be evaluated in conjunction with other findings Moreover results of skin tests alone can never establish the diagnosis or the cause of a particular disease or condition Like other immunologic and laboratory procedures skin tests represent only one link in the chain of diagnostic evidence Correct diagnostic evaluation of their results depends on many other circumstances—in particular the history clinical characteristics and course of the disease and the results of avoidance of and/or re exposure to the suspected agents

To be of value both the type of skin test and the allergens employed must be selected to suit the particular entity and case Correctly selected applied and evaluated skin tests will often be of great aid in the diagnosis and in the discovery of eliciting agents in a wide variety of allergic diseases The correct use of skin tests can also be of assistance in assaying the susceptibilities of individuals and of groups as well as in assaying the sensitizing potentials of sub-

stances Improper or precipitate skin testing often will be useless or misleading—and in some cases dangerous

Patch Tests and Eczematous Reactions in Discovering Eliciting Agents[1]

The significant response to a patch test is an eczematous reaction which usually appears within a few hours and generally reaches its maximum at 48–72 hours

VALUE

The patch test generally is of value in the search for eliciting agents in contact type allergic eczematous dermatitis which includes many cases of allergic occupational dermatitis

PREREQUISITES

1 The *clinical diagnosis* of contact type allergic eczematous dermatitis must be either established or strongly suspected

2 The *history* must have been taken and together with the *appearance localization and course* must point to certain eczematogenic contact allergens as suspects

3 The test materials must be in the proper form concentrations and vehicles The primary irritating or otherwise damaging materials or concentrations must have been excluded by previously obtained data

4 The materials for applying the tests and holding them in place must be at hand (cotton or linen squares impermeable material and adhesive material or the ready made Elastopatches)

5 A detailed record and protocol sheet must have been prepared noting the salient facts of the case the exact nature of the

Only the ordinary patch test is discussed in detail It is the orthodox and most thoroughly standardized method for testing in eczematous allergy although by no means the only one Other methods of applying the agents to the skin such as the mere dropping on dropping on and wiping off holding in place with non occlusive covers and exposure to vapors of volatile substances have been used and found of value in particular circumstances However any deviation from the classic patch test procedure usually requires changes in concentration of the allergen in vehicles in evaluation of responses and in other standards

materials to be applied in the tests the order and sites of their appli cation etc

MATERIALS

Some materials are commercially available but in most instances the physician must prepare his own test materials solutions etc In contrast to scratch and intracutaneous tests as a rule patch tests require no preceding extraction of allergens

The suitable solvents and dilutions for patch testing with many common substances are given in Table 21 This table is based on experience and assays which have demonstrated that patch tests with the specified concentrations and vehicles are innocuous to normal skins i e have no direct or inherent irritating properties in the man ner applied and thus are not primary irritants

Agents and concentrations which without a preceding incubation period regularly produce skin reactions in normal nonhypersensitive subjects who have *never had sensitizing exposure* to the particular agent or to an immunologically related substance are known as *primary irritants* The reaction is caused by direct inherent skin damaging properties of the agent and is not based on a sensitization mechanism or on specifically acquired sensitivity or hypersensitivity of the particular subject s skin

To ascertain the correct concentration for patch testing any un known or untried material must first be standardized by applying safe (i e very high) dilutions to the skins of from 3 to 10 non eczematous nonallergic subjects then if necessary and if there has been no reaction to the higher dilutions progressively greater con centrations can be applied Only agents and concentrations which have produced no reactions in the control subjects are to be used in testing to discover hypersensitivity

In the assaying of new agents the greatest caution is necessary The dangers of such exploratory tests are similar to those described for patch testing in general (p 15) but are of course greatly magnified for first applications of chemicals or mixtures of entirely unknown effects

When *consumer products already in general use for direct and repeated application to the skin* (cosmetics such as powders rouges facial creams lipsticks hand lotions etc stockings socks dresses suits nightwear undergarments shoes gloves furs garters wrist watch straps etc) are being tested *no preliminary testing and assay* of vehicles and concentrations is usually required The articles are obviously not primary irritants for if they were they would not continue in general use for the specified purposes However newly introduced articles of this kind which are not yet in widespread public use may on occasion be primary irritants or strong sensitizers and should be assayed on control subjects before being used in diagnostic testing

An eczematous reaction elicited by patch tests with such ordinary cosmetics or clothing or with articles commonly handled or worn may as a rule be considered evidence of hypersensitivity on the part of the patient There are however exceptions to this rule notably the following

1 Soaps and shampoos soap substitutes (which are used by the public in solution or suspension are not covered over as in the patch test and are usually rinsed off almost immediately)

2 Cuticle removers corn cures peeling remedies materials for hair waving (which are used on a restricted area for the express purpose of dissolving and destroying horny tissue)

3 Rubefacients and counterirritants (which are intended to produce inflammation)

4 Numerous other substances particularly certain volatile agents (cleaning fluids organic solvents in general, bleaches antiperspirants scalp lotions and ointments tincture of iodine etc.)

Articles such as these do not generally produce undesirable clinical irritations when used for their intended purposes and in the usual manner e g without occlusive dressings but are generally primary irritants when applied under the occlusive patch test Substances in this category must be applied either in dilutions previously demonstrated not to be primary irritants on patch testing or by

means of special nonocclusive contact methods such as dropping on and leaving uncovered measured exposure to vapor in vapor cups or test tubes (Fig 1) etc

TECHNIC OF APPLICATION

1 Take a small piece of material (⅛–¼ in wide) cut from the shoe glove suit dress or other material to be tested and moisten it (with water natural or artificial sweat physiologic saline solution etc.) Or take a similar square round or oval piece of soft un starched white cotton or linen (patch) and soak this in the solu tion or impregnate or cover it with the ointment cream etc to be tested. If the material to be tested is solid or particulate take shav ings filings or powdered substance or fine slivers or shreds and place them on the moistened piece of cloth

2 Place the cloth patch on a *grossly normal* skin site

3 Take a somewhat larger (½–1 in) similarly shaped piece of impermeable material (oiled silk gutta percha tissue cellophane etc) and place it over the patch

4 With a still larger piece of adhesive tape fasten the imper meable material and underlying patch firmly to the skin (Fig 2) In cases of hypersensitivity to adhesive tape scotch tape rubber ce ment Frisket Sealtite Sealskin liquid collodion or other adhesive substance must be used Sometimes no form of adhesive substance is tolerated and patches and impermeable covers must be fastened to an arm or leg with windings of ordinary gauze bandage or open methods of testing must be used

A handy ready for use combination of adhesive and impermeable material designed by one of us especially for patch testing can be purchased under the name Elastopatch from Duke Laboratories Stamford Conn (Fig 3)

CHOICE OF SITE SPACING AND NUMBER OF TESTS

In general when a patient suffers from a contact type allergic eczematous dermatitis the entire skin surface has become sensitized and any site is suitable for testing However there are often dif

ferences in the level or degree of sensitivity of different test sites

If a large number of tests is necessary the back is usually the most suitable region For fewer tests or as supplementary test areas the flexor surfaces of the arms and forearms the extensor surfaces of the thighs or other regions can be used

The affected areas and the adjacent skin usually are the most sensitive Therefore if distant tests with strongly suspected materials fail to produce unequivocal positive responses the tests should be repeated on areas nearer to the original dermatosis It is sometimes necessary to apply the test to the actual site of the dermatitis—of course after this has healed As a rule this necessity arises only in cases of the more chronic eruptions

Up to 20 or more patches can be placed in rows on the back (Fig 4) and correspondingly smaller numbers on the thighs arms etc Make a clear record or protocol of the tests applied outlining the exact order and distribution in which they have been placed on the skin (Fig 5)

INSTRUCTIONS TO PATIENT

Instruct the patient to avoid getting the tests wet and to prevent their accidental shifting or removal to remove any patch which is causing strong itching burning or other severe subjective reaction and to report this occurrence at once

TECHNIC OF READING

Remove the patches carefully after 24–48 hours using benzene carbon tetrachloride or other suitable solvent if necessary Wait 15 30 or more minutes to allow any pseudoreaction caused by the removal to subside and the true reaction to become more pronounced (Fig 6) Immediately mark the skin adjacent to each test site carefully placing a number or other identifying designation in line with or around and outlining each test site Use skin marking pencil* indelible ink or small narrow strips of adhesive tape

*Universal marker pencil no 56 American Pencil Company is suitable for this purpose

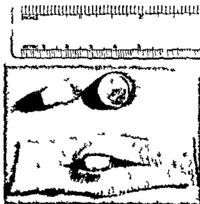


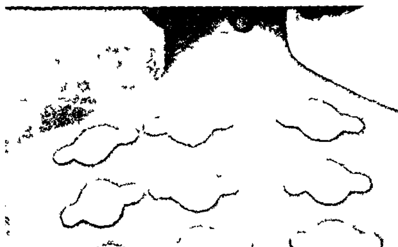
Fig 1 Vapor cup for testing volatile materials *above* cup and absorbent cotton *below* absorbent cotton and cup in place under adhesive tape This type of test is *not* a patch test *It has* been used extensively for the study of *primary irritant* vapors but has not yet been standardized as well as the patch test for the study of *allergenic* materials

Fig 2 Application of patch tests One patch test has been applied the second is being applied The cloth square moistened with the test solution has been applied the adhesive tape—on the under side of which the cellophane disc has been attached—is about to be placed over the square (From Sulzberger M B *Dermatologic Allergy* [Springfield Ill Charles C Thomas Publisher 1940])



Fig 3 Elastopatch (Duke) *Above* cellophane elastoplast and cotton square shown separately *below* the same materials in proper position for actual testing →

Fig 4 Three rows of four patches each have been placed on the back (For sample protocol sheet for this series of tests see Figure 5)



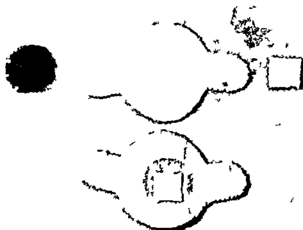


Fig 5 Sample protocol sheet for patch test series illustrated in Figure 4

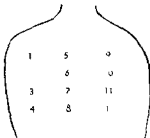
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APPLIED -16 46 t back

PAT H TESTS WITH THERAPEUTI AGE ITS



1 C 1 t 10% i p rol tum
2 S 1f p ipit t 10% i p t 1 um
3 Whitfi ld i tme t
4 S li yli id 10% i p t 1 tum

5 B i acid 10% i p t 1 tum
6 B i 10% in pet 1 tum
7 il f d 10% i pe rol tum
8 Oli il i

9 L nolin i
10 Liquo b i d t g 5 i p t 1 um
11 Hyd ry um ammo i um, 10% in p t 1 tum
12 S 1f thi 1 5% in p t 1 tum

READ

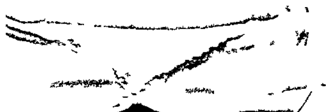


Fig 6 Patch test sites on back a few minutes after removing patches The adhesive tape remnants and the mild peripheral erythema in this case permit fairly exact location of the actual test sites It is usually preferable to mark each test site with skin marking pencil immediately after removal of the patch (From Sulzberger M B *Dermatologic Allergy* [Springfield Ill Charles C Thomas Publisher 1940])

EXCLUSION OF PSEUDOPOSITIVE REACTIONS—The following nonspecific false or pseudopositive reactions are to be distinguished from the significant eczematous response

1 Reactions to pressure from hard particles or substances under the patch

2 Infection or maceration under the patch

3 Adhesive tape irritation from trauma of removal from primary irritation or from hypersensitivity to adhesive (usually separated from the central patch area by the intervening area of contact with the covering cellophane or other occlusive material)

4 Primary irritant effects of the applied material alkali and acid effects etc

5 Stains due to dyes or colored materials (lipsticks nail polish dyes dyed objects) or to other staining agents (silver nitrate potassium permanganate etc)

6 Other dermatoses appearing under the patch either by coincidence or owing to the nonspecific trigger effect of the patch test (Kobner s isomorphic reaction)

The effects of pressure trauma of tearing off the plaster etc generally disappear or diminish within an hour When it is necessary to rule out such reactions have the patient wait and reread the reactions 30–60 minutes or more after the patches have been taken off if required repeat the readings at 24 and 48 hours Most pseudopositive reactions abate within the first few hours whereas true positive allergic reactions often persist or increase at least for 48 hours and sometimes up to several weeks Indeed in exceptional cases no visible allergic reaction is present until 48 or more hours after removal

Some reactions at the patch test sites appear only after five days others after two or more weeks Such reactions are probably *not equivalent to the 24–48 72 and 96 hour reactions and cannot be regarded as proof of a pre existing hypersensitivity* for whenever the appearance of reaction is delayed for *more than four days* it is

probable that *a local or general increase of cutaneous sensitivity was produced by the test application itself* It is a general immunologic rule that a latent period of more than four days commonly repre sents the *incubation* period required for boosting a pre existing sensitivity or for *developing a new sensitivity* When this is true any number of repetitions of the test will elicit reactions in the usual 24–48 hours instead of the five or more days required for the development of the first reaction

RECORDING AND EVALUATION OF POSITIVE REACTIONS

Significant reactions to patch tests present the changes *charac teristic of eczema* A system for recording the intensities of these reactions is given in Table 1

When questionable reactions occur the test should be repeated after an interval and in a different site the test material should first

TABLE 1 —SIGNS FOR RECORDING DEGREES OF PATCH TEST REACTIONS (After Br Bloch)

Sign	Reaction
0	no reaction
(+)	mildest erythema
+	erythema
++	erythema and edema and/or beginning papulation or vesiculation
+++	fully developed vesiculation papulation edema bullae
++++	strongest reaction—denudation necrosis etc.
	Intermediate reactions may be designated by combinations of these symbols E.g erythema and slight edema or a very few papules = + to ++
	Questionable reactions may be indicated by ?

be checked for adequate freshness concentration etc If the ma terial is one incriminated by history course and other findings but still elicits no reaction the test should be applied closer to the affected areas or on the affected areas themselves after healing has taken place

CONTRAINDICATIONS AND DANGERS

The patch test is one of the safest of clinical immunologic tests *provided* the foregoing directives are followed exactly When the correct concentrations vehicles etc are used the few unavoidable sensitizations which occur will be *confined to individuals who would in all probability have become sensitized on clinical exposure to the agent in question*

The untoward effects which can follow improper use of the patch test may be of local and/or of general character Observance of the five following rules will help avoid undesirable effects

1 Patch testing to discover possible eliciting agents must be confined to cases of allergic contact type eczematous dermatitis

2 Never test in a haphazard fashion Never test only as a gesture or placebo Confine the tests to substances which are truly suspect in the given case and which cannot be conclusively incriminated or exculpated by other methods

3 Reduce the risk of producing flare ups dissemination or pro longation of the eruption by refraining from testing severe or wide spread dermatoses during their active phases

4 Always be sure of the inherent innocuousness of your material When applying new or unknown substances avoid the hazards of producing a new sensitization of causing excessive local or general ized damage and of poisoning through absorption These hazards can be reduced by ascertaining in advance that the substance in the particular concentration vehicle etc is harmless to normal subjects

5 Whenever possible do not use cosmetically important areas when applying tests which may cause long lasting changes or dis figurement (pigmentation staining scarring) Whenever possible avoid the face and the neck arms and decollete areas in women

Other Uses of Patch Tests

In addition to its recognized value in the search for eliciting agents of allergic eczematous dermatitis there are several other

and industrial substances cosmetics creams lotions clothing leather, dyes finishes waterproofing materials objects used in games and sports jewelry other articles of adornment cleansers insecticides insect repellents fungicides water repellents fireproofing materials moldproofing materials etc external medicaments etc)

METHOD I INDEX OF SENSITIVITY OF A POPULATION — Patch tests are performed on the largest possible sample of a popula tion which has had *previous exposures* to the substances in question Such testing is designed to discover the incidence of the population s previously acquired sensitivities to the particular agents This method is suitable for testing only those products which contain ingredients to which a population may be assumed to have been generally and regularly exposed

METHOD II SENSITIZING INDEX (SENSITIZING POTENTIAL) OF AGENTS —This method measures the relative capacity of an agent to sensitize persons who have not previously been exposed to the substance in question Patch tests (or other contact applications inunction dropping on etc) are performed with the materials be ing investigated applying *potentially sensitizing* concentrations of the agents to the largest obtainable sample of normal presumably *not previously exposed* persons Retests are performed 28 or more days later using the agents either in their original state and concen tration or in the form and concentration of usual or expected ex posure in occupation in consumer uses etc

This method of determining the sensitizing potential in our opinion represents the *only adequate procedure* for testing newly introduced substances i e substances to which there has been no opportunity for general exposure and for which therefore there is no pool of previously exposed subjects

EVALUATION —In the case of consumer articles intended for use on or next to the skin reactions indicating sensitization of even *ore person* in *several thousand* may well signify an *unallowable poten*

tial hazard to the public For other substances such as occupational and therapeutic agents the permissible percentage of reactions may sometimes be set considerably higher depending on the particular value indispensability uses and opportunities for protection against the particular substance

Tables 3 and 4 show the large samples required i e the great number of individuals who must be tested to obtain statistically valid

TABLE 3 —NUMBER OF SUBJECTS REQUIRED IF THERE ARE NO POSITIVES IN THE SAMPLE TO PREDICT WITH A 95 OR 99 PER CENT LIKELIHOOD THAT THE POPULATION RATE DOES NOT EXCEED CERTAIN DESIGNATED VALUES (noted in left hand column)

Ma m m P rm ss bl P rc t g f React P pul t	R q d N f S bjects fo L k l hood f 95%	99%
0 01	29,978	46 083
0 1	2 994	4 603
0 5	597	918
1 0	298	459
2 0	148	228
3 0	98	151

From Henderson C. R. d Riley E C. Certa n stat st l co d rat ns in p ch testing J I vest. Dermat. 6 27 230 June 1945

data on the potential innocuousness of a material or product under investigation

In bioassays of potentially allergenic consumer products industrial agents and other articles the following points must constantly be borne in mind

1 The patch test is designed and has been calibrated to study only *allergic hypersensitivity of eczematous type its usefulness for determining primary irritancy or direct damaging effects is not yet established*

2 Even in cases of true allergic eczematous sensitization, the patch test will serve only as a screening measure to evaluate the *relative* sensitizing potentials of two or more substances Thus the patch test can help decide that substance A is less likely to sensitize than substance B and on this basis that A should be selected in pref erence to B etc

and industrial substances cosmetics creams lotions clothing leather dyes finishes waterproofing materials objects used in games and sports jewelry other articles of adornment, cleansers insecticides insect repellents fungicides water repellents fireproofing materials moldproofing materials etc external medicaments etc)

METHOD I INDEX OF SENSITIVITY OF A POPULATION — Patch tests are performed on the largest possible sample of a population which has had *previous exposures* to the substances in question Such testing is designed to discover the incidence of the population s previously acquired sensitivities to the particular agents This method is suitable for testing only those products which contain ingredients to which a population may be assumed to have been generally and regularly exposed

METHOD II SENSITIZING INDEX (SENSITIZING POTENTIAL) OF AGENTS —This method measures the relative capacity of an agent to sensitize persons who have not previously been exposed to the substance in question Patch tests (or other contact applications inunction dropping-on etc) are performed with the materials being investigated applying *potentially sensitizing* concentrations of the agents to the largest obtainable sample of normal presumably *not previously exposed* persons Retests are performed 28 or more days later using the agents either in their original state and concentration or in the form and concentration of usual or expected exposure in occupation in consumer uses etc

This method of determining the sensitizing potential in our opinion represents the *only adequate procedure* for testing newly introduced substances i e substances to which there has been no opportunity for general exposure and for which therefore there is no pool of previously exposed subjects

EVALUATION —In the case of consumer articles intended for use on or next to the skin reactions indicating sensitization of even *one person* in *several thousand* may well signify an *unallowable poten*

usually tested is inadequate for estimating the probable incidence of skin reactions in the millions or infinitely large groups of potential users of certain products

BIOASSAY
1 Patch tests with consumer goods industrial materials and other products will *help* to discover and to exclude from use certain powerful eczematogenic allergens
2 Such tests will help to estimate the relative sensitizing potentials of two or more agents
3 Negative results of patch tests never completely exonerate substances in regard to their possible production of eczematous sensitivity and clinical dermatitis

PATCH TESTS IN ANALYSIS OF SUBSTANCES FOR CONTENT OF PARTICULAR ALLERGENS (BIOANALYSIS OF MATERIALS)

Patch tests can help ascertain whether a mixture or a product contains particular allergens in such concentration and form as to be capable of eliciting eczematous reactions in hypersensitive persons

METHOD—Several persons *previously proved* to have a high degree of eczematous contact type hypersensitivity to a certain allergen are patch tested with the product or mixture under investigation If the product or mixture contains a sufficient quantity of the allergen in a form capable of producing an eczematous reaction positive patch tests will be obtained in the selected hypersensitive individuals Absence of reactions to the mixture or product indicates absence of allergen in the form or quantity necessary to produce the skin reaction

EXAMPLE—A small amount of formaldehyde was introduced during one stage in the manufacture of certain widely used paper towels and

paper tissues During subsequent stages of the manufacturing process the formaldehyde was both washed out and neutralized However, the manufacturer wished to make *certain* that there was no remaining trace of formaldehyde which might produce dermatitis in even the most hypersensitive of users Four test subjects with strongly positive patch test reactions to a 5 per cent solution of formalin were selected and the paper tissues and towels under investigation were applied as patch tests The absence of reactions demonstrated (probably more accurately than any available method of chemical analysis) that the finished towels and tissues did not contain formaldehyde in quantity or form capable of producing eczematous dermatitis even in hypersensitive subjects These towels and tissues have now been used with impunity by millions of persons over many years

PATCH TESTS IN SELECTION OF EMPLOYES (BIOASSAY OF PERSONS)

Pre employment patch testing has not yet found general acceptance but theoretical considerations and practical experience indicate that it may be of considerable value under appropriate conditions In industries or occupations in which allergic contact type eczematous dermatitis is a significant cause of trouble it is only logical that employes should be *selected* in such a way as to reduce the incidence of sensitization dermatitis (in addition of course to taking *all other accepted preventive measures)*

It is recognized that persons with excessively moist excessively dry and fissured or excessively greasy skin as well as persons with previous or existing dermatitis or certain skin infections (folliculitis furuncles intertrigos etc) are likely to be abnormally susceptible to particular forms of occupational skin damage [8] Similarly persons who have *previously* become *sensitized to several common eczematogenic allergens* have been shown to be on the whole more susceptible to future eczematous sensitizations to other allergens

Whereas there appears to be no significant difference between the fair and the dark complexioned whites Negroes as a group are generally less susceptible than whites to allergic eczematous sensitizations

METHOD I TO DETERMINE GENERAL SUSCEPTIBILITY TO ECZEMATOUS SENSITIZATION AND CONTACT TYPE DERMATITIS — In selecting employes for occupations notorious for a high incidence of allergic eczematous contact type dermatitis those candidates who represent the poorest risks can be discovered by (*a*) careful history directed toward the previous occurrence of certain dermatoses (*b*) careful examination of the entire skin for the presence of certain

TABLE 5 — COMMON ECZEMATOGENIC ALLERGENS FOR PRE EMPLOYMENT PATCH TESTING

1. Nickel sulfate 5% in water
2. Sodium arsenate 10% in water
3. White ammoniated mercury 5% in petrolatum
4. Potassium bichromate 0 5% in water
5. Butesin picrate 5% ointment (Abbott) as is
6. Procaine 2% in water
7. Formalin 5% in water
8. Whitfield s ointment N F 50% in petrolatum
9. Potassium iodide 50% in petrolatum
10. Paraphenylendiamine 2% in petrolatum
11. Para red deep 44 as is
12. Poison ivy Lederle s acetone extract (8-13% solids) diluted 1 5 000 with acetone
13. Turpentine 50% in olive oil
14. Flit (proprietary product) 25% in olive oil
15. Tincture of Pyrethrum as is

dermatoses and predisposing conditions and (*c*) patch testing with a selected series of commonly encountered eczematogenic allergens Table 5 lists a number of allergens suitable for pre employment patch testing Individuals who present *no* eczematous allergic reactions to any members of this list are *in general* less likely to become sensitized to new occupational eczematogenic allergens than are individuals who react to two or more members

METHOD II TO DISCOVER PRE EXISTING HYPERSENSITIVITY TO ALLERGENIC AGENTS OF PARTICULAR OCCUPATION — It is well known that certain occupations inevitably entail exposures to certain notorious allergenic agents

Thus, fur dyers will be exposed to aniline dyes rubber workers to accelerators and vulcanizers plastic workers to formalin florists to chrysanthemums primroses and other allergenic plants farmers in the

United States to ragweed and timothy hair dressers barbers painters nurses physicians surgeons dentists housewives etc. to the many allergenic substances of their occupations

Patch tests with eczematogenic allergens characteristic of a particular occupation will demonstrate whether or not the candidate for employment is already allergic to one or more of the agents in question and is therefore a poor risk for the particular job

PRE EMPLOYMENT PATCH TESTING

1 Will add another method to help screen out certain employes particularly likely to become sensitized by notorious occupational allergen
2 Will not guarantee that employes will escape nonallergic occupational dermatoses
3 Will not guarantee that no allergic dermatitis will develop in patch test negative persons
4 Will not if properly executed, sensitize those who would not in all likelihood soon have become sensitized by normal occupational exposures

Two principal criticisms have been leveled at this method of testing with the particular agents of expected exposures The first is that a negative result of the pre employment test with a given occupational substance does not rule out the possibility that the individual may later become sensitized to that very substance This is undoubtedly true and considerably limits the usefulness of this method compared with method I which tests for general susceptibility to *future* sensitization rather than for *pre existing* hypersensitivity to *particular* agents. Nevertheless a positive patch test reaction to a given occupational substance does help to prevent the costly error of em

ploying an individual already hypersensitive and therefore obviously unsuitable for that particular occupational exposure

The second criticism is that such pre employment patch tests with the allergens of a particular occupation may *sensitize* some of the candidates to those very allergens Whereas this too is true it by no means reduces the usefulness of the method for those candidates who become sensitized by the single application of a properly applied and executed patch test with *correct vehicle and dilution* would *undoubtedly soon have become sensitized by clinical and occupational exposures* Medically socially and economically the sooner such marked susceptibilities to sensitization are discovered the better for the worker the employer and all others concerned

Scratch Tests and Intracutaneous Tests for Wheal Responses

These tests are employed mainly to discover eliciting agents in those allergic conditions associated with the *urticarial* type of response to skin tests and hereafter called urticarial allergy Here the significant response to both scratch and intracutaneous tests is a *wheal and/or flare* with localized itching occurring within a few minutes The reaction generally reaches its maximum in from 5 to 20 minutes

The uses and the significance of results of scratch and intracutaneous tests are roughly equivalent since the shock tissue tested and the form of reaction are identical There are however numerous practical differences resulting from the variations in the two technics Most important is the quantitative difference in the amount of allergen reaching the shock tissues It has been estimated that to produce equivalent reactions the amount or concentration of allergen applied for the scratch test must be 1 000–10 000 times that for the intracutaneous test

Each method presents certain advantages and disadvantages In general the intracutaneous method is *much superior* to the scratch method Whereas the scratch method has the advantages of relative safety availability of test materials ease of application and econ

omy the results achieved with the extracts we have used have often been unreliable This has again been demonstrated by recent studies undertaken at our suggestion by Dr Robert Narins at the New York Skin and Cancer Unit In these as yet incomplete studies scratch tests produced highly irregular and unreliable results (marked variations in reactions from site to site in the same subject on the same day and in the same subject from day to day etc)

However because of potential dangers inherent in the intracutaneous method in the hands of the nonspecialist we were faced with the choice of recommending the decidedly poorer scratch test method or recommending that the nonspecialist should not himself carry out any tests for immediate wheal reactions In order not to deprive the nonspecialist of all possibilities of carrying out such tests we decided to suggest the use of the scratch method when testing for immediate wheal reactions is necessary

Scratch Tests and Wheal Reactions in Discovering Eliciting Agents

VALUE

Scratch tests are indicated in the search for eliciting agents in

1 Hay fever (seasonal allergic rhinitis or coryza)
2 Nonseasonal allergic rhinitis or coryza due to *inhaled* allergens
3 Allergic asthma (bronchial asthma) due to *inhaled* allergens

Scratch tests are occasionally indicated in the search for the eliciting agents in

1 Allergic coryza (rhinitis) due to foods or drugs
2 Allergic asthma due to foods or drugs
3 Infantile eczema (atopic dermatitis in the infant)
4 Gastrointestinal allergies due to foods or drugs
5 Parasitic infestations

Scratch tests are rarely indicated in the search for eliciting agents in

1 Atopic dermatitis in older children in adolescents and adults (disseminated neurodermatitis prurigos etc)

2 Urticaria due to foods to organ extracts (liver insulin etc)

3 Urticaria due to drugs

4 Allergic headaches

Scratch tests are generally of *no value* in the search for eliciting agents in any diseases and dermatoses other than those specified above including

1 Coryza due to infection

2 Allergic asthma due to infection and asthma due to nonallergic mechanisms

3 Chronic urticaria

4 Angioneurotic edema

5 Allergic eczematous contact type dermatitis

6 All nonurticarial drug reactions and other nonurticarial dermatoses and all nonurticarial reactions and diseases of organs or systems other than the skin etc

WHY THE SCRATCH TEST RATHER THAN THE INTRACUTANEOUS TEST

For reasons previously given we are of the opinion that in testing for eliciting agents in suitable *urticarial allergies* the general physician will prefer to use the scratch test rather than the intracutaneous method. Some details forming the basis for this opinion are elaborated here

1 As a rule in general practice and in specialities other than allergy skin tests for urticarial responses are not likely to be used with sufficient frequency for the physician to acquire the habit of unconsciously avoiding all possible errors in intracutaneous testing The necessary precautions will probably never become routine and second nature to the general physician as they do to the allergist.

2 The technic of the scratch test is so simple and safe that it can be carried out by almost any physician or technician without long special training

3 Severe infections although rare with either method are even less probable with the scratch test technic

4 There is no necessity for the heat sterilization of instruments Wiping the scratch test scalpel borer or needle with 70 per cent alcohol suffices

5 There is no danger of syringe contamination i e of false positives due to adherence to the imperfectly cleaned syringe or needle etc of minute quantities of allergens previously used

6 Procurement and storage of allergens are much simpler for scratch tests than for intracutaneous tests

7 Economy Practically no special equipment is necessary, there is no breakage and practically no cost of upkeep

8 More scratch tests than intracutaneous tests can usually be applied at one sitting

9 Most important *there is much less risk of producing severe or dangerous reactions* with the scratch test than with the intracutaneous test constitutional reactions following scratch tests are most uncommon

Despite these advantages of the scratch over the intracutaneous test the latter presents certain features which make it *superior to the scratch test* (p 37)

PREREQUISITES

1 The diagnosis of one of the allergic diseases specified as suitable for scratch testing must have been established or strongly suspected

2 The history must have been taken and together with the clinical picture and course must point to certain allergens as suspects

3 The allergenic test substances must be at hand in proper form vehicles and concentrations Primarily or inherently irritating primarily urticariogenic or otherwise locally or systemically damaging agents concentrations and vehicles must have been excluded by previously obtained data

4 The equipment and materials for carrying out the tests must be at hand

5 A detailed record must have been made noting the facts of

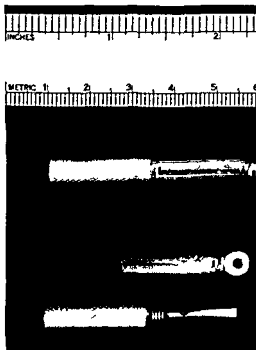


Fig 7 Screwdriver type instrument for producing scratches *above* with cap in place for carrying *below* with cap off ready for use (Suggested by Dr Lewis Webb Hill Boston)

Fig 8 Borer type device for use in scratch testing This device is probably the easiest to handle for the novice to produce uniform scratches

Fig 9 Five vertically arranged rows of three scratch tests each. Pencil markings in the periphery permit identification of the 15 sites (For sample protocol sheet of tests and recorded reactions see Figure 10)

NAME: M H

A E: 14

DATE OF TEST: Feb 12 1946

SITE OF TESTS: b ck

RATCH TESTS:

O	1	camel dander
+	2	cat dander
	3	rabbit dander
T	4	goat dander
+	5	dog dander
	6	c ttle dander
O	7	k pok
O	8	tobacco
O	9	cotton
	10	orris root
	11	mixed feathers
+	12	sheep wool
O	13	pyrethrum
O	14	silk
	15	horse dander

1 4 7 10 13

^ 5 8 11 14

3 6 9 12 15

Fg 10 Sample protocol sheet of tests and reactions recorded in scratch test series shown in Figure 9



Fig. 11. Scratch test with powdered protein allergens. Step I (*above*): A drop of N/10 sodium hydroxide has been placed on the skin of the flexor aspect of the forearm. Screwdriver-type instrument is held for scratching. Step II (*below*): The screwdriver-type instrument has been pressed into the skin through the drop of sodium hydroxide. The scratched site is now ready for application of the allergen.



the case the exact nature of the materials being applied in the tests the order and sites of their application etc

6 The materials for preventing untoward reactions (see p. 90) must be at hand and ready for immediate use

a) Several ampules or a bottle of solution of epinephrine 1 1 000 (The bottle should be kept in the dark and should be marked with date of preparation solutions which have turned brownish or violet must be replaced)

b) A sterile 1 cc. tuberculin syringe and hypodermic needle

c) A rubber tourniquet

d) An examining table couch sofa or bed

ALLERGENIC MATERIALS

COMMERCIAL EXTRACTS—Practically all the common protein allergens used in scratch testing are commercially available in powder or in liquid form For those materials accepted by the Council on Pharmacy and Chemistry of the American Medical Association and included in the 1946 edition of *New and Nonofficial Remedies* see pages 212 f

MATERIALS NOT COMMERCIALLY AVAILABLE—If no reliable commercial extract is available the suspected material can be used as *clinically encountered, provided dangers of serious infection are excluded* However in every test with such material of *unknown or untried* urticariogenic properties the scratch test on the patient must be controlled by *applying the material in an identical manner to the normal skin of two or three nonallergic subjects* Only if the urticarial reaction in the patient is significantly greater than that in the normal control subjects can the conclusion be drawn that the patient has an urticarial form of *hyper*sensitivity to the particular substance

Many materials regularly produce urticarial reactions in normal, *non hypersensitive* subjects who have presumably never been exposed to the particular agent or to an immunologically related substance These materials are known as primary urticariogenic agents or primarily or *inherently irritating* agents (primary irritants) *The reaction is* produced by a direct urticariogenic effect (i e the inherent wheal produc

ing action) of the agent and is *not* based on a *specific sensitization* or an exceptional sensitivity on the part of the patient Such primary urticariogenic agents are of course *not suitable for scratch testing to discover the existence of an urticarial form of allergy* or to discover the eliciting agents in cases of hay fever allergic rhinitis asthma infantile eczema prurigos atopic dermatitis etc. It is noteworthy that many substances which are commonly *ingested* or *injected* without causing clinical urticarial eruptions (codeine morphine atropine etc) are primary urticariogenic agents when applied as scratch or intracutaneous skin tests (This demonstrates that the *usual* effect of a material ingested or otherwise administered systemically does not necessarily indicate the urticariogenic or nonurticariogenic action of that material applied from without and in relatively high concentrations directly to the small vessels of the normal skin)

The fullest possible precautions must be taken not to apply agents to the skin which might cause serious infections (nonsterile dusts danders hairs furs etc) or which might elicit other types of primary damage to the skin Therefore before agents with entirely unknown effects are applied as scratch tests preliminary assays and tests must have excluded the possibilities not only of primary urticariogenic action but *particularly* of infection or other serious local or systemic damage

CHOICE OF SITE SPACING AND NUMBER OF TESTS

If many tests are to be done the back is usually the most suitable region For a smaller number of tests or as supplementary test areas the flexor areas of the arms and forearms the extensor areas of the thighs or other regions can be used

Depending on the area of normal skin available if proper precautions are observed 20–50 scratch tests can be performed at one sitting

Immediately mark the skin adjacent to each row of test sites carefully with ink or skin marking pencil using a number or other identifying designation (Fig 9) Make a clear record or protocol of the tests applied arranging them in the identical order and dis

tribution in which they have been placed on the skin (Fig 10) The tests can be placed in rows of 5–10 each spacing each test at least 4–5 cm from the nearest one in any direction

It is not uncommon to see wheal and flare reactions at scratch test sites *adjacent or near* the site of *a strongly positive reaction* This regional coreaction or sympathetic reaction is probably due to traumatic fixation of the allergen absorbed and disseminated from the positive site Spacing must be sufficiently wide to reduce the incidence of such false positives

In most cases of true urticarial hypersensitivity the entire skin has become sensitized and is suitable for scratch testing However, there often are differences in the level of sensitivity of different sites

TECHNIC OF APPLICATION

Make a superficial scratch in the skin with the blunt side of the tip of a scalpel or with a needle a borer or a screwdriver type instrument The scratch should either be round (1–2 mm in diameter) or be about 3 mm long and just deep enough to incise only the *epidermis i e not* deep enough to produce bleeding

Apply the allergen or allergenic extract to the scratched area. To insure application to the scratched site it may be necessary to distribute the liquid containing the allergenic material over a small area surrounding the scratch itself by gently spreading it with the particular utensil (toothpick dropper etc) used for transferring the allergen to the skin

The various categories of allergens are applied as follows

Powdered Allergenic Extracts Apply 1 drop of N/10 sodium hydroxide to the selected site Make the scratch through the drop of sodium hydroxide (Fig 11) By means of the flat tipped end of a toothpick transfer an approximately pinhead sized quantity of allergenic powder from the vial or bottle to the drop of N/10 sodium hydroxide on the skin Use the same flat tipped end of the toothpick to mix the powder and the sodium hydroxide for about five seconds

Use a fresh toothpick for each application Never place the toothpick used for one allergen in the container holding another allergen

Once it has touched the hydroxide solution or the skin never return the toothpick to the original container

Liquid Allergenic Extracts After making the scratch first apply 1 drop of the extract with a medicine dropper (or the dropper cap supplied with the bottle containing the extract) or by means of a glass rod capillary tube or collapsible tube To make certain that the extract comes in contact with the scratch use the tip of the dropper or rod to distribute the extract gently over a small area surrounding the scratch

Materials Not Commercially Available When testing with suspected materials which have not been *specially prepared* for scratch testing dry and powdered materials or liquid materials are applied as indicated for powdered extracts

If the suspected article is cloth or other fabric cut a piece about 1 sq cm apply it to the scratch and add enough N/10 sodium hydroxide to wet the entire piece and to leave a slight excess of liquid on the skin If the suspected article consists of fibers hairs etc but would be ruined by cutting off a small square of material pull out a few fibers or hairs (e g wool from a sweater hair from a fur piece etc [4]) and apply them to the scratch adding enough N/10 sodium hydroxide to wet the material and to leave a small excess of liquid on the skin

If the suspected material is solid (wood metal plastic etc) take shavings filings slivers shreds or powdered substance and place them on the drop of N/10 sodium hydroxide on the skin Add enough sodium hydroxide solution to the area to wet the material and to leave a small excess of liquid on the skin

INSTRUCTIONS TO PATIENT

Instruct the patient to sit or to lie still until the reading of the tests and to announce any development of severe itching or swelling at the test site and any sneezing

First rule out presence of anthrax bacilli tetanus bacilli tubercle bacilli pathogenic cocci etc by appropriate cultures and other methods

TECHNIC OF READING

Before reading wait a full 20 minutes after the scratch test has been applied. This period is usually optimal for the development of the true reactions and often allows the minor nonspecific traumatic effects to subside.

EXCLUSION OF PSEUDOPOSITIVE REACTIONS.—No [illegible] should be drawn from the *unconfirmed* [illegible]. Every test with a positive or questionable reaction [illegible]

The following are the important [illegible] positive reactions which are to be discounted.

1 Wheal and flare reactions due to primary [illegible] effects of test materials

2 Erythema and whealing due to dermographism [illegible] ical irritability of the patient's skin. (In such [illegible] control scratch test will show similar reaction," [illegible] the skin is unsuitable for scratch testing at that [illegible]

3 Simulated erythema caused by stains of the [illegible] (red or brown) materials

4 Other skin reactions caused by primary [illegible] effects (For example in patients with an alkali [illegible] *not altogether uncommon in patients with* [illegible] N/10 sodium hydroxide may cause a whitish [illegible] of the skin [not a raised or spreading wheal] [illegible] of erythema The presence of this form [illegible] detected by the fact that virtually *all* the sites to [illegible] sodium hydroxide has been applied show [illegible] more on examination at 24 or more hours [illegible] crust which may persist for a week to 10 days, [illegible] the former central whitish area produced by the [illegible])

5 Coreaction of adjacent or distant sites, [illegible] semination of allergen from one scratch [illegible] other scratch sites

RECORDING AND EVALUATION OF REACTIONS

The significant positive reactions should appear within a few minutes and must be either *edematous*, i e urticarial and/or have a definite red flare The intensities of the urticarial reactions are generally graded as shown in Table 6

TABLE 6—SIGNS FOR RECORDING DEGREES OF SCRATCH TEST REACTIONS

Sign	Reaction
0	(no sensitivity) no reaction
(+) or ±	(absent or questionable sensitivity) mildest erythema no wheal
+	(slight or absent sensitivity) pinhead sized or slightly larger wheal surrounded by little or no erythema
+ +	(slight to moderate sensitivity) wheal 1 cm or 2–4 times original traumatic papule in diameter surrounded by slight erythema
+ + +	(moderate to marked sensitivity) wheal 2 cm or 8–10 times original traumatic papule in diameter usually with few or small pseudopods and surrounded by slight erythema
+ + + +	(very marked sensitivity) wheal 4 cm. or 10–15 times original traumatic papule in diameter usually with pseudopods or sunburst outlines paler than normal skin and surrounded by erythema often accompanied by itching

Intermediate reactions may be designated by combinations of the above symbols E g wheal 3 cm in diameter surrounded by erythema = + + to + + +

Questionable reactions may be designated by ?

In case of questionable reactions the test should be repeated later in a different site If the result is again questionable the test should be repeated on a different day at a different site and if possible with an allergenic extract of different manufacture Such repetition is also desirable when a material which has been strongly incriminated by history clinical picture and course fails to elicit a reaction In these instances also the use of the stronger intracutaneous test is often indicated

CONTRAINDICATIONS AND DANGERS

Properly used the scratch test is one of the safest of clinical immunologic tests *Severe constitutional reactions are rare* The occurrence of new sensitizations from exposure to an allergen in the scratch test has not been reported

The untoward effects which can follow improper use of the scratch test may be of local and/or general character For emphasis we repeat that observance of the following rules will aid in avoidance of undesirable effects and reactions

1 Do not perform a scratch test with an allergen which on the basis of history clinical picture and course has been conclusively proved to be the eliciting factor This simple rule excludes unnecessary testing and materially reduces the risk of severe constitutional reactions

2 Fresh solutions of epinephrine 1 1 000 and a sterile hypodermic syringe and needle should be available whenever scratch tests are being performed to counteract quickly the signs and symptoms of a severe reaction (severe itching or swelling at the test site sneezing wheezing hives swelling of the lips tongue or eyelids rhinitis asthma shortness of breath abdominal cramps or other untoward effect)

3 When using nonsterile materials such as dusts danders hairs furs etc rule out the presence of anthrax bacilli gas gangrene bacilli tetanus spores pathogenic cocci etc before applying

4 Do not use scratch tests if infection is present elsewhere (impetigo furuncles *vaccination* etc) Postpone tests until well after the infection has cleared

5 Any materials which have not previously been used for scratch testing must first be assayed on normal control skins to rule out primary urticariogenic and primary irritant effects

6 Do not use an instrument with which you are unfamiliar or which is too sharp Instruments which are likely to cut deeper than the epithelium are unsuitable for producing the scratch Such a cut (instead of a scratch) may produce nonspecific traumatic reactions

may increase the risk of infection and may also inhibit a specific allergenic reaction if the exuding and/or the clotted blood impedes penetration of the allergen to the blood vessels in the cutis

7 Reduce the risk of errors by immediately marking the skin next to each scratch with ink or pencil by having a carefully prepared protocol sheet ready to fill in on reading and by waiting a full 20 minutes before reading results

8 Do not scratch test patients with a tendency to keloidal scarring or during eruptive stages of other dermatoses particularly psoriasis lichen planus mollusca contagiosa and warts If you do do not be surprised if you later see the scratch sites occupied by keloids or lesions of the particular dermatosis (Kobner s isomorphic reaction Fig 12)

Intracutaneous (Intradermal) Tests and Wheal Reactions in Discovering Eliciting Agents

VALUE

The indications for and the value of the intracutaneous test *parallel* those of the scratch test Moreover as they are simply different technics for studying the same form of reaction of the same shock tissue a detailed description of manner of application reactions dangers etc would entail needless repetition Since the scratch test is the one we recommend for general use the pertinent facts have been submitted in that section The reader interested in intracutaneous testing should first acquaint himself with the entire section on scratch testing

Despite their many similarities there are distinct differences between scratch and intracutaneous tests The advantages of the scratch test over the intracutaneous test for general use by nonspecialists have been described The obverse or the particular superiorities of the intracutaneous test over the scratch test is discussed here

In the intracutaneous test for wheal responses the solution of *allergen is injected into the skin as superficially as possible instead* of merely being placed on a scratch or abrasion Like the response

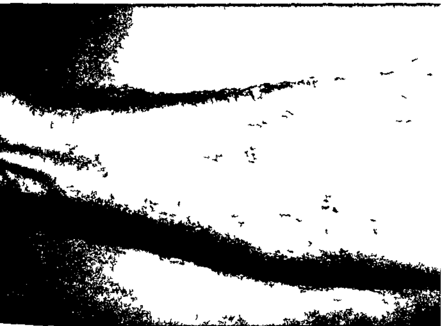


Fig 12 Isomorphic (Kobner's) phenomenon Typical lichen planus lesions appearing at the sites of scratch tests performed several months earlier (From Sulzberger M B *Dermatologic Allergy* [Springfield Ill Charles C Thomas Publisher 1940])





Fig 13 Intradermal test on upper arm Step 1 (*left*) The inner aspect of the upper arm is firmly grasped between thumb and fingers This keeps the skin taut at the projected site of injection Step 2 (*right*) The tip of the needle is inserted superficially into the skin just far enough to raise the skin slightly in a pinhead sized area Next step is actual injection of *allergenic* material



Fig 14 Intradermal test on back Skin is held taut between thumb and index finger Needle tip has been inserted superficially into skin just far enough to raise skin slightly in a pinhead sized area

to the scratch test the significant response is a *wheal and flare* usually appearing within 2–10 minutes

WHY THE INTRACUTANEOUS TEST IS PREFERABLE FOR PARTICULAR USES

Hay fever asthma and other respiratory allergies due to inhaled substances are the principal allergic conditions in which specific hyposensitization by the method of *injection* proves most valuable Specialists treating numerous patients with these particular allergies will therefore have at hand the sterile solutions of allergens neces sary for intracutaneous testing This fact together with the following advantages of intracutaneous testing makes it the method of choice for many allergists

1 The intracutaneous test is more sensitive with the same concentration of allergen the subcutaneous test will elicit responses in skin sites having degrees of sensitivity which are lower than those necessary for a response to the scratch test

2 It is the more precise and quantitative method of administer ing allergen and thus of demonstrating variations in degrees of sensitiveness

3 It may be less disturbing to the patient for in the hands of the experienced operator the procedure is often speedier and less traumatizing than the scratch

4 It permits the use in injection treatment of precisely the same allergenic extract as that used in the test

Although these advantages do not outweigh the dangers and disadvantages for the *nonspecialist* (p 27) they make clear why the specialist in allergy often will prefer the intracutaneous to the scratch test

Moreover the intracutaneous method may be valuable when the scratch test fails to elicit a response with substances strongly incriminated as eliciting agents by the history and clinical evidence Finally in all research and investigation requiring *exact quantitative skin test exposures* the intracutaneous method of administration is *indispensable*

Still another common use of the intracutaneous injection is its general use when testing the skin for 24–48 hour inflammatory responses to extracts of micro-organisms viruses toxins etc as in tuberculin and trichophytin tests Frei test, Schick and Dick tests etc.

PREREQUISITES

The prerequisites to intracutaneous testing to discover eliciting agents include the careful history clinical evaluation and other preparatory steps described in the directions for the scratch test (p 28) The following materials are also required

1 The materials for preventing or counteracting severe or constitutional reactions

2 Ethyl alcohol 70 per cent or isopropyl alcohol 70 per cent and sterile wipes or cotton should be used to prepare the sites

3 A Luer tuberculin type syringe of 1 cm capacity equipped with 26 gage ½ in needle should be provided for *each* test substance It is preferable to mark and reserve each syringe and needle for a particular solution of allergen At any rate no syringe or needle may be re used until it has been thoroughly cleansed of residual testing extract in *cold* running tap water (hot water will coagulate the protein and clog the needle) and then sterilized in boiling water or in an autoclave

ALLERGENIC EXTRACTS

Fluid extracts of the pollens epidermals and foods for use in intracutaneous testing for urticarial responses are manufactured by Wyeth Incorporated These are available with cartridge syringe and replaceable cartridge (Tubex) vials The physician who does not use Wyeth cartridge vials or other commercial extracts (p 212) must either prepare his own extracts or obtain them from the laboratory of the allergy clinic with which he is associated The therapeutic fluid extracts of the pollens epidermals and foods described for hay fever and for bronchial asthma may be used *in the proper dilutions* for intracutaneous testing

However as stated previously it is our opinion that the intra

cutaneous method of testing is not generally suited to the routine of the nonspecialist

CHOICE OF SITE SPACING AND NUMBER OF TESTS

The lateral aspects of the upper arms or thighs are the sites commonly used In general the back and trunk should not be used for these sites do not permit the successful use of a tourniquet to prevent threatened general reactions (p 90)

Whenever a number of intracutaneous tests are performed at one sitting the test sites should be arranged in vertical rows along the upper arm lower arm thigh or leg There should be a minimum space of 1 in (2–3 cm) between sites No more than one row of six tests should be done at a time with 10 minutes intervening between the placing of each row It is preferable to limit the number of tests at one sitting to a maximum of 18 In children only one half this number should be performed at a session

TECHNIC OF TESTING

METHOD OF INJECTION —To facilitate the insertion of the point of the needle the skin should be kept taut The operator can grasp the patient s skin posteriorly with his left hand and thus tense the skin while injecting with his right hand (Fig 13) In areas where this is not feasible the skin can be kept taut between the index and third fingers of the operator s left hand (Fig 14)

AMOUNT INJECTED —The amount should be as small as pos sible generally not more than 0 01–0 02 cc Larger amounts *used in intracutaneous tests for 24–48 hour inflammatory responses* are *contraindicated* when testing for wheal responses because they often produce traumatic growing wheals and false positive readings

INSERTION OF NEEDLE —The sterile syringe and needle con taining the solution of allergen is held in the right hand of the operator somewhat as though it were a pencil The tips of the fourth and fifth fingers of the right hand rest on the skin of the patient while the point of the needle is slowly inserted *as superficially as possible* into the skin using a twisting motion produced by rotating

the syringe barrel on its long axis between the thumb and the index finger With rotation less force is needed for the needle point to enter the skin After penetration the bevel of the point should face *downward* with the eye of the needle held tightly against the underlying tissues (Fig 13) (In a correctly administered test the penetration of the skin is so shallow that leakage might occur were the eye of the needle allowed to face upward)

When the extract has been properly injected a minute scarcely visible often blanched wheal is seen The needle is then withdrawn and the site again cleansed with 70 per cent alcohol *No other antiseptics are applied* The skin at each test site becomes slightly elevated above the surrounding surface as the positive reaction grows this elevation becomes more prominent owing largely to the developing zone of erythema which surrounds the injected fluid When fully developed the wheal will often present a dimpled or pigskin like appearance the dimples caused by the binding down of the epidermis at the hair follicles

TECHNIC OF READING RECORDING AND EVALUATION OF REACTIONS

The positive immediate wheal reaction will develop within 2–10 minutes The time is somewhat variable being briefest in the most sensitive patients

The reading and recording of reactions is the same as that for scratch tests (Table 6)

EXCLUSION OF PSEUDOPOSITIVE REACTIONS —As with scratch tests no conclusions should be drawn from unconfirmed results Every test with positive or questionable reaction should be repeated Moderate slight and negative reactions indicate tests with stronger extracts If positive reactions cannot be verified the original reaction is doubtful and little reliance should be placed on it Such unverifiable reactions should be regarded rather as false positives They often may be caused by air in the syringe injected with the extract or by traces of some other allergen to which the patient is

sensitive and which was not properly removed when the syringe was cleaned

The other causes of false or pseudopositive responses are given in detail under scratch tests (p 33) Many of these are even more likely to occur in intracutaneous testing

CONTRAINDICATIONS AND DANGERS

Those described for the scratch test (p 35) are applicable with *much greater emphasis here* General or constitutional reactions which are rare in scratch testing may quite easily occur on intra cutaneous testing with extracts to which the patient is very sensitive A history carefully obtained before beginning any tests often will place the physician on guard and will indicate either that weaker solutions than usual should be used or that *no intracutaneous tests* should be employed

Some allergists hold that, in patients suspected of great hyper sensitivity, it is wisest to refrain from intracutaneous testing at least until scratch tests with the suspected agents have been performed

Too many tests at a time may lead to a general reaction for a cumulative effect may develop should the patient happen to be sensitive to a number of the allergenic extracts used Tests should be limited therefore to six or less at a time waiting at least 10 minutes before giving others If more than two in the row of six give positive reactions further testing should be postponed until another day The patient must be kept under direct observation throughout the period of testing and for at least 20 minutes after the final test so that any evidence of a beginning general or constitutional reaction may be noted and properly handled (The handling of the general reaction is discussed in Chapter 2)

Intracutaneous Tests and 24–48 Hour (Tuberculin-Type) Reactions in Discovering Eliciting Agents

A method equivalent to the scratch test was first introduced by von Pirquet for demonstrating the *late inflammatory* 24–48 hour skin response to tuberculin and similar extracts However the

intracutaneous method, because of its greater accuracy soon replaced the scratch technic At present the scratch test has been practically superseded by the intracutaneous test for 24–48 hour tuberculin type responses Fortunately in intracutaneous testing for tuberculin type sensitivity the dangers of the immediate form of constitutional reactions are negligible for allergens producing tuberculin type hypersensitivity rarely produce allergies with severe general forms of immediate reactions and usually fail to elicit urticarial responses of the skin or other organs

The *significant skin response* to intracutaneous test for late tuberculin type reaction is an inflammatory erythematous papular reaction appearing *within a few hours and generally reaching its maximum at 24–48–72 hours* (Fig 15) Any immediate or wheal reaction appearing within a few minutes is disregarded in reading this test

VALUE

The intracutaneous test for 24–48 hour inflammatory reaction is of practical value in demonstrating cutaneous sensitization from present or past exposure to causal agents of *lymphogranuloma venereum chancroid coccidioidosis, insect bites, malleus sporotrichosis trichinosis tuberculosis tularemia undulant fever* and numerous other infections It is usually of less practical value in demonstrating cutaneous sensitization from past exposure to causal agents of actinomycosis blastomycosis erysipeloid fungous infection (trichophytons epidermophytons microsporons monilias) leprosy parasitic infestation (echinococcus) and other infections (staphylococci streptococci)

PREREQUISITES

1 Careful clinical examination must first have led to the suspicion or presumptive diagnosis of an infection or infestation which is known to produce late tuberculin type cutaneous sensitization

2 The history must have been taken and together with the appearance localization and course must point to certain bacterial



Fig 15 Late tuberculin type reaction to sporotrichin in a case of sporotrichosis Central erythematous papule is surrounded by an area of erythema and induration (*In reactions* to tuberculin itself there is usually no such *markedly raised* central papular lesion instead the *entire reaction* consists more or less of an area of *erythema* and induration)

fungous virus parasitic or insect allergens as the suspected agents

3 The test materials including whatever control materials may be required must be ready in proper form vehicles and concentrations

4 A detailed record must have been made noting the facts of the case the exact nature of the materials being injected and the order and sites of their injection etc

5 Although the danger is remote the materials for counteracting the immediate form of constitutional reactions should be at hand.

6 Ethyl alcohol 70 per cent or isopropyl alcohol 70 per cent and sterile wipes or cotton should be used to cleanse the skin sites

7 Luer tuberculin type syringes of 0 25 0 5 or 1 cc capacity equipped with 26 gage ¾ in. needles should be provided for each test substance and for each control material

8 All precautions for sterility and cleanliness of syringes and materials must be rigorously observed

ALLERGENIC MATERIALS

COMMERCIAL EXTRACTS —Most materials of established value in testing for 24–48 hour late tuberculin type reaction are *commercially available* The particular materials used in skin testing to ascertain exposure to the different pathogenic agents are listed under the respective disease entities

Some of the commercial preparations of the specific agents used in testing for the 24–48 hour type of reaction are prepared cultured diluted or suspended in materials which are themselves allergenic and occasionally capable of eliciting cutaneous reaction of the late tuberculin type *Intracutaneous tests with such agents must be checked by injection of a control material* which has been prepared in the same manner as the test material but which does not contain the specific allergens of the pathogenic agent for which the test is designed (blank control uninoculated broth etc)

The control test should be performed simultaneously with and in a *manner identical* to that of the test itself in the *same test subject* and in a site *symmetrically situated with the test site* (on

the other arm thigh etc) Control materials are often furnished by the manufacturer in the same package as the test material In tests with materials in which a control test is obligatory (e g lymphogranuloma venereum antigen of nonhuman origin) the *test should be considered positive only if its reaction is significantly greater than the reaction at the control site*

Materials Not Commercially Available—When no appropriate commercial extracts are available *it is no* generally advisable for the physician to attempt to prepare the necessary extracts or vaccines in his office Such new extracts can be used only after they have been *thoroughly investigated for lack of general toxicity and cutaneous primary irritancy for sterility and for specificity* to mention only a few of the steps necessary for standardization of new preparations

CHOICE OF SITE SPACING AND NUMBER OF TESTS

Skin tests for 24–48 hour tuberculin type reactions are best performed on the flexor aspect of the forearms or on the lateral surfaces of the upper arms When these areas are not available or suitable the tests can be placed on the extensor aspects of the thighs or if necessary on the back or any other part of the glabrous skin As a rule the entire skin has become sensitized and is suitable for testing At times there are minor variations in the levels of sensitivity of different sites but these are generally of little practical significance

If a series of tests is to be done (e g., with graded dilutions of tuberculin) the tests can be spaced at about 5 cm intervals Mark the skin adjacent to each test site immediately after injecting the test materials using small strips of adhesive ink or skin marking pencil Remember that the marks must remain until the time of reading 48–72 hours later

TECHNIC OF TESTING

Method of Injection—As in all injections the skin is first cleansed with 70 per cent alcohol Except for the greater amount

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4 A ...

5 ...

6 ...

8 All ...

ALLERGENIC MATERIALS

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The significant response
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persists for many hours or even days With some materials (tuberculin trichophytin) the reaction sometimes tends to be rather diffuse and consists of a plaque of erythema induration and edema about 2–5 cm in diameter With other types of materials (Frei antigen sporotrichin) the reaction tends to be more localized and consists of an erythematous papule which may or may not be surrounded by an areola of erythema and which may have a pustular or necrotic and later crusted center

It is noteworthy that in occasional instances and particularly with certain types of antigens (e g tuberculin and trichophytin) there is further development or recrudescence of the reaction for several days to weeks and even months Often these later phases take on the appearance of any type of skin eruption to which the patient is subject (isomorphic reaction)

It is also not unusual for the papular inflammatory responses to be accompanied or followed by other morphologic forms such as *eczematous* responses lichenified and scaly areas follicular annular or bullous reactions purpuric lesions etc The significance of these associated or consequent reactions is not yet clear

Exclusion of Pseudopositive Reactions—The following false or pseudopositive reactions are to be discounted

1 Reactions due to primary irritant effects of the test materials (e g from accidental contamination of the particular vial or bottle from which the material is derived)

2 Reactions due to infection at the test site (e g from nonsterile extracts inadequate cleansing or accidental introduction of microorganisms at the time of the test)

3 Reactions produced by syringe contamination resulting from adherence to the syringe or needle of minute quantities of extracts previously used Some false reactions in this category are caused by dilution error in which the same syringe previously used for injecting a concentrated solution is used for injecting a higher dilution of the material (The vestiges of the concentrated solution can interfere with the accuracy of the higher dilution)

In other instances remnants of an entirely unrelated test material which had previously been used in the syringe cause false positives

4 Reactions produced by extracts which have deteriorated because of faulty storage or which are used later than the specified expiration date (Deterioration may cause irritative pseudopositives but more commonly leads to false negatives)

5 Reactions not produced by the specific allergens but by the

TABLE 7.—SIGNS FOR RECORDING DEGREES OF 24–48 HOUR TUBERCULIN TYPE REACTIONS TO INTRACUTANEOUS TESTS

Sign	Description
0	(response no greater than at control site) no reaction
(+)	(inconclusive as evidence of hypersensitivity) mild erythema and infiltration in area less than 0 5–1 cm in diameter or slightly greater response than at control site
+	(definite but slight hypersensitivity) definite erythema and infiltration in area 0 5–1 5 cm in diameter or significantly greater response than at control site
++	(moderate to marked hypersensitivity) erythema and infiltration 1 5 3 cm in diameter
+++	(marked hypersensitivity) erythema and infiltration sometimes with central vesiculation surrounding edema etc in area 3–4 cm in diameter
++++	(very high degree of hypersensitivity) strongest and largest reactions sometimes with vesiculation pustulation necrosis surrounding erythema and edema lymphangitis etc.

Intermediate reactions may be designated by combinations of the above symbols

Questionable reactions may be indicated by ?

medium or vehicle in which the specific component is contained This pseudoreaction must be ruled out by using control tests

RECORDING AND EVALUATION OF REACTIONS

The significant reaction is an inflammatory one which persists for several days or longer The readings are customarily made at 48 or 72 hours and the intensities of the tuberculin type reaction are generally graded as shown in Table 7

In questionable reactions the test should be repeated in a different site the material first being checked for adequate freshness concentration etc *If the result is again questionable the test should* be repeated in a different site and if possible with a different extract of the material (prepared by a different manufacturer etc) Such repetition is also desirable whenever an allergen which is *strongly incriminated by history or clinical data fails to elicit a* skin reaction

CONTRAINDICATIONS AND DANGERS

Properly used the intradermal test for 24–48 hour tuberculin type reactions is a safe clinical immunologic test The untoward effects which can follow improper use of this test may be of local and/or systemic character The chances for severe reactions vary with the type of test material used and with the type and the degree of sensitivity of the subject

The more severe local reactions consist of great induration erythema edema and tenderness at times associated with lymphangitic involvement and even regional lymph node enlargement. Crusting and necrosis ulcerations and scarring may follow severe reactions

The milder systemic manifestations include headache fever malaise nausea and eruptions of erythema nodosum or erythema multiforme character The more serious ones include activation or dissemination of the original disease process in internal organs and/or skin (e g tuberculous foci after tuberculin test) and activation or dissemination of cutaneous lesions to previously unaffected areas (e g secondary fungous eruptions or ids after trichophytin test)

Observation of the following rules will aid in avoidance of undesirable effects and reactions

1 Do not test any case unnecessarily

2 Start testing first with a safe dilution one which reasonably can be assumed not to produce a severe reaction *in the* particular patient

3 Use only fresh and uncontaminated extracts and sterile syringe and needle to avoid infection and pseudoreaction.

4 Do not test while cutaneous infection is present elsewhere on the body (impetigo vaccination furuncles etc.) Wait until *after the infection has cleared*

5 Do not test during active phases of acute eruptions during which there is danger of severe aggravation and dissemination of lesions (e g acute and vesicular dermatophytid) Wait until the acute manifestations have subsided

6 Be particularly careful with subjects known or suspected of having visceral foci which would cause serious trouble should they become activated (e g active tuberculosis)

Other Uses of Intracutaneous Tests

INTRACUTANEOUS TESTS IN ASCERTAINING INCIDENCE OF CUTANEOUS SENSITIVITY (INDEX OF SENSITIVITY OF A POPULATION)

Intracutaneous tests for 24–48 hour tuberculin type reactions with extracts prepared from micro-organisms parasites or insects are performed on a population or a group representative of a population This method is suitable for testing groups in schools hospitals camps districts cities etc for sensitivity to agents of a disease to which the particular group may be assumed to have been exposed It has two principal uses

1 In epidemiologic studies to ascertain the incidence of present and/or past exposures to infectious micro-organisms fungi viruses etc or of exposure to certain biting insects

EXAMPLE.—Intracutaneous tests with lymphogranuloma venereum vaccine or with Ducrey vaccine may be given to ascertain the incidence of present and/or past infection with lymphogranuloma venereum or with chancroid The approximate incidence of infection by the agents of these venereal diseases in a given group can thus be easily determined without any laboratory procedures

2 In immunologic studies to ascertain the normal or usual level of cutaneous sensitivity produced by present and/or past exposures to infectious micro organisms (bacilli cocci fungi or viruses) or by such exposures to infesting parasites or to biting insects

EXAMPLE—In the average community in the United States a large proportion of the population sooner or later undergoes infection with tubercle bacilli Such infection usually produces cutaneous sensitization to tuberculin which in most adults can be demonstrated in the 24–48 hour inflammatory reaction to intracutaneous test with a 1 5 000 dilu tion of tuberculin (OTK) In urban populations such reaction in adults can at present be considered evidence of a normal level of sensitivity Once such a *normal* level is ascertained in a given population a pro nounced deviation in either direction may be of differential diagnostic significance (see tuberculoderms)

INTRACUTANEOUS TESTS IN DIFFERENTIAL DIAGNOSIS OF TUBERCULODERMS

This test is of limited differential diagnostic value in distinguishing between different types of tuberculoderms The level of tuberculin sensitivity in an individual is ascertained by intracutaneous tests for 24–48 hour late reaction with quantitative serial dilutions of tuber culin (1 10 to 1 1 000 000 OTK) The method is described in detail in the section on tuberculoderms The finding of hyper sensitivity (hyperergy) normal sensitivity (normergy) or hyposensitivity (*hypoergy or relative anergy*) *to tuberculin* is then used as evidence for or against the diagnosis of a particular type of tuber culoderm *In general* it may be stated that reaction at 1 100 000 or 1 1 000 000 dilution indicates the so-called *hyperergic* group of tuberculoderms (lupus vulgaris tuberculosis colliquativa tuber culosis lichenoides) whereas hyposensitivity or no reaction until the concentration is 1 100 or greater indicates a torpid more or less benign type of tuberculosis or some other condition known to be hypoergic or relatively anergic to tuberculin (sarcoids granu loma annulare etc)

INTRACUTANEOUS TESTS IN DISCOVERING ANTITOXIC IMMUNITY

The significant response is an *absence* of skin reaction at 48 hours This lack of reaction indicates an immunity to the injected toxin which is usually based on the presence of adequate amounts of circulating and/or skin fixed antitoxin

VALUE

The intracutaneous test is generally of great value in demonstrating the presence or absence of antitoxic immunity in diphtheria (Schick test) and particularly in determining the efficacy and duration of prophylactic immunization This test may be useful in scarlet fever (Dick test)

The Schick test is of value in ascertaining the incidence of past infection with diphtheria in groups of individuals (schools hospitals communities towns cities) The Dick test is of limited value in similar epidemiologic studies of scarlet fever

MATERIALS

The materials used in testing for antitoxic immunity in diphtheria and in scarlet fever are commercially available These preparations are listed in the sections on diphtheria and scarlet fever

TECHNIC OF TESTING

Preparation and technic of injection are the same as those for intracutaneous testing for 24–48 hour tuberculin type reactions Conventionally 0 1 cc of the toxin is injected intracutaneously

Intracutaneous tests to ascertain antitoxic immunity are best performed on the flexor aspect of the forearm or arm In case these areas are not available or suitable for testing the tests can be done on any other part of the glabrous skin Antitoxic immunity is generally present on all parts of the skin surface although different sites may differ somewhat in their degree of sensitivity or immunity

TECHNIC OF READING

In persons who are *not immune* to the injected toxin a reaction usually develops at 24–48 hours and reaches its height at 48–72

hours The optimal time for reading tests is generally at 48 hours The reaction is characterized by an area of erythema and induration about 1–2 cm in diameter This reaction usually persists for six to eight days and then becomes scaly and subsides leaving an area of brownish pigmentation which lasts for several weeks

As a rule no significant skin reaction is noted in immune individuals The reader will recognize that reactions of skin sensitivity to

TABLE 8.—INTERPRETATION OF SKIN REACTIONS TO TOXINS AND TO SENSITIZING ALLERGENS OF MICRO-ORGANISMS

	Positive Skin Reaction	Absent Skin Reaction
Schick test (Diphtheria toxin)	Indicates *absence* of previous immunizing exposure to diphtheria toxin	Indicates previous immunizing exposure to diphtheria toxin
Dick test (Scarlet fever toxin)	Indicates *absence* of previous immunizing exposure to scarlet fever toxin	Indicates previous immunizing exposure to scarlet fever toxin
Tuberculin test Trichophytin test Frei test Certain insect allergens etc.	Indicates previous sensitizing exposure to the allergens of the respective micro-organisms or insects *	Indicates *absence* of previous sensitizing exposure to the allergens of the respective micro-organisms or insects

* Positive and negative results here indicate previous exposure and sensitization and thus have a significance analogous to eczematous skin responses to patch tests and to wheal responses to scratch and intracutaneous tests

toxins signify *exactly the reverse* of the reactions of tuberculin type sensitivity to allergens of infective agents (Table 8)

EXCLUSION OF PSEUDOPOSITIVE REACTIONS.—The following false or pseudopositive reactions are to be discounted

1 Pseudo-Schick and pseudo Dick and similar pseudoreactions A skin reaction which is positive despite presence of antitoxic immunity may appear at 12–24–48 hours and be somewhat similar in appearance to positive Schick and Dick tests However such

pseudoreactions are *not due to the toxin* but usually represent a 24–48 *hour tuberculin type reaction* to the *allergenic* fractions of the injected material i e a sensitivity to the protein allergens or to the toxoid etc. Pseudoreactions tend to disappear more quickly than true Schick or Dick reactions and usually do not leave as much scaling and pigmentation Many pseudoreactions can be recognized by performing a control test with anatoxin or toxoid i e heat or formalin denatured toxin If the skin reaction was a pseudoreaction which appeared despite the presence of antitoxic immunity the control test with anatoxin will usually elicit a skin response as strong as that at the site of injection of the toxin On the other hand if the positive reaction was a true positive due to toxin and denoting absence of antitoxic immunity the response to the control with ana toxin will be negative or significantly less than that at the toxin site

2 Early urticarial reactions These are due to an urticarial type of sensitivity to the test material and are not in any way indicative of the presence or absence of antitoxic immunity Their significance is as yet unknown

3 The first four pseudoreactions listed for 24–48 hour tuber culin type reactions to intracutaneous tests (p 46)

CONTRAINDICATIONS AND DANGERS

The intradermal test to ascertain antitoxic immunity is a safe clinical immunologic procedure provided it is properly employed Untoward effects which may be produced by these tests can be re duced to a minimum if only fresh uncontaminated extracts and sterile syringes and needles are used

INTRACUTANEOUS TESTS IN DEMONSTRATING PRESENCE OF TOXIN BY SPECIFIC NEUTRALIZATION BY ANTITOXIN

When positive this test is generally of great diagnostic value in differentiating between true scarlatinal and pseudoscarlatinal erup tions (Schultz Charlton or blanching test) The method and technic are described in the section on scarlet fever

OPHTHALMIC TEST

Instead of the skin the eye can be used as a test organ to ascertain the state of sensitivity of the individual and of his mucous membranes Since many allergenic materials placed in the conjunctival sac rapidly penetrate to the blood vessels no scratch or injection is necessary

The ophthalmic test is most useful for *ascertaining the level of* the urticarial or immediate form of sensitiveness of the mucous membranes to air borne protein allergens and to horse serum or other serums The sensitivity of the conjunctivae often parallels that of mucous membranes elsewhere There is also often a corresponding sensitivity of the skin thus ophthalmic tests and scratch *or intracutaneous tests frequently elicit parallel results However* the sensitivity of the eye is in some cases significantly less and in other cases significantly greater than that of the skin and ophthalmic sensitivity may exist even in the absence of cutaneous sensitiveness and vice versa

VALUE

The ophthalmic test may be of diagnostic value in establishing the presence of a respiratory allergy such as that in hay fever It may be of particular value when the skin test to pollens is negative although the clinical history suggests pollen allergy

In the *severe and more dangerous forms of horse serum allergy* which usually occur in patients with atopic or familial allergies and which are often present without preceding demonstrable exposure to horse serum *there is a tendency for the ophthalmic mucosa to be sensitive to horse serum* whereas in the *milder forms of horse serum allergy* such as may occur in nonatopic persons following exposure to therapeutic serums *the ophthalmic mucosa often fails to become sensitized* although the skin develops sensitiveness (demonstrable by wheal reactions to scratch or intracutaneous tests) Thus *the ophthalmic test is of inestimable value in the most*

important clinical task of differentiating between these two forms of serum allergy A positive ophthalmic test serves as a warning of a potentially dangerous degree of clinical hypersensitivity to foreign serum and indicates that the serum should either be withheld or administered only when absolutely necessary and then with the utmost caution

The ophthalmic test is generally of no value in determining sensitiveness to foods or to bacteria Its usefulness is also limited because many allergens cannot safely be used in the eye and because only a few agents can be tested at a time since no more than one positive reaction in each eye is possible at any one session And of course since only immediate urticarial type reactions can be evaluated the eye will not serve as a test organ for eczematous or tuberculin type sensitivities

PREREQUISITES

As discussed under intracutaneous and scratch testing a complete and focused history must first be obtained The further prerequisite that *each allergen must be applied as a scratch test before being placed in the eye* is necessary to discover any high degree of sensitiveness which would preclude use in the eye

Untoward general reactions may readily occur from ophthalmic tests with highly potent allergens Therefore the materials for preventing such general reactions must be at hand and ready for immediate use (p 29) In addition to the usual materials a *1 10 000 dilution of epinephrine should be ready for instillation into the eye to check the local reaction*

ALLERGENIC MATERIALS

The extracts or solutions used for ophthalmic testing in hay fever or other respiratory allergies are the same as those used in intracutaneous tests (p 38) Sometimes powdered allergens can be employed such as those used in scratch tests However the use of pure pollens is not advised because it may lead to general

severe reactions Available pollen extracts in both aqueous and powder form and pure pollen are listed in the section on hay fever

In ophthalmic testing for serum sensitivity the proper dilutions of serum in sterile physiologic saline are 1 10 000 1 1 000 1 100 and 1 10 The weakest concentration is used first

TECHNIC OF TESTING

It is best to use a 1 cc Luer type syringe and 26 gage needle for instilling the allergen solution into the eye After drawing approximately 0 05 cc of the allergenic extract or serum solution into the syringe the *needle is removed* from the syringe barrel and the testing material deposited in the eye at the outer canthus (A sterile medicine dropper is sometimes used but we have found this both awkward and wasteful)

Extreme care must be taken in choosing the proper strength of material The highest dilution of pollen extract or of horse serum or other foreign serum must be used first If negative results are obtained a slightly stronger concentration may be tried.

TECHNIC OF READING

Positive reactions like other urticarial reactions are usually apparent in 2–10 minutes There is itching and erythema beginning at the outer canthus The erythema may extend first to the conjunctiva of the lower lid and then to that of the upper lid. The lower inner quadrant may become injected. Such reactions are termed mild.

If the erythema extends from the lower inner quadrant to the outer or to both lateral quadrants the reaction is termed *moderate* (Fig 16) Involvement of the whole conjunctiva indicates a *marked* reaction

Overdosage is indicated by sneezing coryza nasal obstruction intense injection and edema of the whole conjunctiva and even reaction of the cornea. A general or constitutional reaction may occur requiring hypodermic injections of epinephrine in addition to instillation of epinephrine into the eye



Fig 16 Ophthalmic test Moderate reaction in left eye fairly marked injection and slight edema of conjunctiva mainly the lower inner quadrant Note difference between the left (test) eye and the right (control) eye

CLINICAL TESTS

GENERAL REMARKS

The method of avoidance and re-exposure and those of clinical evaluation history and appropriate tests constitute the four pillars at the foundation of the search for eliciting agents Observation of the patient s responses to elimination or reduction of exposure to a suspected allergen and *when necessary* to controlled re exposures is not only a great diagnostic aid but in a certain sense the *acid test of the correctness of the deductions based on all other findings*

Here quite literally the proof of the pudding is in the eating. If the eating of tapioca pudding never produces a clinical reaction in the patient and if the avoidance of tapioca does not improve his condition then tapioca cannot be adjudged the important responsible allergen, *regardless* of the results of history skin tests or other investigations

The allergens in each case are selected on the basis of all previous evidence—clinical diagnosis localization and manifestations of the disease the implications of the history and course and other data

The procedure of avoidance and/or re exposure is extremely useful even in those forms of allergy which give reactions to skin tests The effects produced by avoidance of and/or re-exposure to suspected agents will sometimes be noted *before* skin testing clinical observations then are checked by *subsequent skin tests* Or the avoidance of exposure or the re exposure may be carried out *after* skin testing and *subsequent clinical observations* serve to support or to weaken the testimony of the skin tests

But the greatest usefulness of the method of avoidance and re exposure lies in its being the essential procedure—almost the *sine qua non*—in the many forms of allergic disease in which *no known form of skin test has been found to be of value* (most urticarias many food allergies most drug reactions etc) The details of this method in different forms of allergy are discussed under the particu lar disease entities At this point only a few broad rules will be presented

TECHNICS —The methods can be divided into two principal categories

1 The methods by which the physician observes the effects of spontaneous (natural or fortuitous) changes in exposure These include such seasonal or intermittent exposures as naturally occur in the case of pollenizing plants flowers or other plants some food articles insects etc exposures to sun or heat or cold exposures to winter or summer clothing winter or summer furnishings heating, etc. exposures to the allergens characteristic of games sports or other seasonal activities exposures to certain occupational allergens

2 The methods in which the physician acts as *deus ex machina* and deliberately produces the avoidance of or exposure to suspected agents

CLINICAL TESTS WITH INHALANT SUBSTANCES

In the search for eliciting agents the physician often observes the effects of *changes of environment* The patient is ordered to move to another place (another bed room apartment house city climate) If the change in immediate environment from the home to another dwelling is quickly followed by improvement and if the improvement continues until interrupted by a return to his home the implication is strong that one or more eliciting allergens is present in the home These home allergens may be contact agents such as a cosmetic insecticide or furniture polish inhalants such as pollens dust feathers animal danders or even ingested agents such as drugs or foods

Benefit from climatic change however may point to a bacterial or fungal agent. Similarly the disappearance of an allergic dermatosis respiratory allergy or other allergic disease on interruption of the patient s attendance at shop or factory suggests the presence of an occupational eliciting allergen particularly if a return to the occupation is promptly followed by a return of the allergic disease

CLINICAL TESTS WITH FOOD

In a manner similar to that adopted in studying the effects of environment the physician can study the effects of *diet* Of necessity except in young children and bed patients these changes cannot be as sharp clearcut and complete as is often the case in changes of physical environment The dietary changes are best accomplished by forbidding foods which are suspected either on the basis of the patient's own history or because they are known to be common offenders or for both reasons If the patient becomes symptom free the foods which have been removed may be returned (seriatim) to the diet a subsequent recurrence of symptoms affords suggestive evidence of the allergenic importance of each food Thus two factors are involved in the clinical test with foods (1) the exclusion from the diet of foods suspected on particular grounds or on their allergenic reputation and (2) the evaluation of the effects of such exclusions and of subsequent renewed inclusions These effects should be systematically recorded by the keeping of a *food diary*

RESTRICTIVE DIETS —In the simplest form of restrictive diet the items removed are those which careful questioning of the patient brings to light as proved or suspected offenders either in the past or in the present. To this list of prohibitions may be added those foods which produce positive skin tests Frequently the causes of a food allergy particularly in childhood may be determined by these relatively simple and convenient procedures

When such methods are unsuccessful the diet may be formulated by instructing the patient to avoid those foods commonly recognized as the most important offenders both in incidence and in severity of symptoms *Egg, wheat milk seafood nuts seeds and chocolate* are by general agreement the chief allergenic foods It is this list—the foods as such as well as all dishes prepared with them or containing even traces of them—that must be rigorously avoided *All other foods are permitted* It is not enough to instruct the patient to eliminate milk egg and wheat from his diet He must be provided with

[illegible] information on foods [illegible] which contain these items and [illegible] in a child's diet, for example [illegible] [illegible].

The following lists will be found [illegible] common offenders. Such a list should [illegible] addition to the verbal explanations given.

EGG-FREE DIET

Avoid

Eggs [illegible]
Egg-containing foods such as
  [illegible] flour mixes for home cooking
  Pancakes, [illegible] cakes, pastries
  Waffles, [illegible], pretzels
  Macaroons, meringues, [illegible]
  Cakes, cookies, unless known to be egg-free
  [illegible], unless known to be egg-free
  Ice cream and sherbets, unless known to be egg-free
  Cornstarch, cream candies, fondants
  [illegible]
  [illegible] with glazed crust
  [illegible], meat dishes containing [illegible]
  [illegible] with egg [illegible]
  [illegible] chicken

WHEAT-FREE DIET

Avoid

Wheat, whole wheat, cracked wheat flour in breads, waffles, [illegible] pastries, pies, cakes, cookies [illegible] [illegible]
Corn bread, unless known to be wheat-free
Rye bread, unless known to be wheat-free
Soy bread, unless known to be wheat-free
G[illegible]
Breakfast cereals, dry or cooked, containing wheat [illegible]
C[illegible] containing wheat
Bread [illegible] with wheat
Coffee substitutes containing wheat, beer, etc.
[illegible] such as sausages, frankfurters [illegible]

MILK-FREE DIET

Avoid

[illegible] cream as such, and in [illegible]
[illegible] cream sauces
[illegible] for home cooking
[illegible] or corn
[illegible]
[illegible] in
[illegible]
[illegible]

SEAFOOD FREE DIET

Avoid
Fish and shellfish fresh canned smoked pickled fish liver oils and concentrates in vitamin preparations
Fish and shellfish stews bisques broths soups salads hors d oeuvres caviar roe
Avoid licking labels which often contain a fish glue adhesive

NUT POOR DIET

Avoid
Nuts of all types also peanuts (a legume) and cottonseed meal in health and laxative breads
Nut crumbs on cookies cake icings ice cream
Candies containing nuts
Salad oils lard substitutes margarines made of cocoanut cottonseed or peanut oils (many are so made—inquire of the grocer) olive oil permitted

Individuals highly sensitive to nuts are often allergic to seeds such as cotton seed flaxseed mustard (by external application in poultices as well as when ingested as foods) beans peas Legumes such as peas beans lentils are often allergenic factors in the patient sensitive to nuts but some patients tolerate legumes such as peanuts despite high degrees of nut sensitivity

The purpose of each of these diets is to eliminate one of the most commonly offending foods If two or more foods are to be eliminated the lists are combined When successful there should be alleviation or disappearance of symptoms within *one* or *two* weeks The banned foods may then be returned to the diet *singly* with *48 hours between additions* so that any appearance of symptoms may be the more readily traced to the responsible food If the symptoms persist despite the dietary limitations a food diary (p 62) should be kept while the patient is still following the restricted and simplified diet Should no exciting factors be evident from a close study of the diary over a *three week period* the procedure may be abandoned

SEMISTARVATION DIET —A much more drastic contraction of the diet may be necessary in those instances in which restrictive measures prove unavailing or the acuteness of symptoms does not justify the time required to study their effects The patient may be placed on a semistarvation diet which consists of

DAYS 1–3	DAYS 4 5 *Add*	DAY 6 *Add*	DAY 7 *Add*
Boiled rice	Carrots	Beef or lamb	Grapefruit
Butter	Beets		Prunes
Weak tea	Lettuce		Pears
Cane sugar			
Salt			
Lemon			

There is no limit to the amount of rice permitted The weak tea should be limited to four cups daily and for the first three days the remaining items limited to amounts just sufficient to render the rice and tea palatable Ascorbic acid is generally nonallergenic and may be added in amounts up to 1 000 mg daily The vegetables are added on the fourth day if the patient has shown improvement and the remaining foods are added as specified If improvement has not occurred by the fourth day the rice diet should be changed to a diet of milk butter baked white potato and salt for three days with no limitation of quantity After the third day proceed as outlined. If the patient s condition does not warrant the prolongation of such a drastically reduced diet after the first or rice, diet has failed to pro duce improvement he may be returned to his ordinary diet for three days and then restricted to the milk and potato regime

At the end of the seventh day other foods may be added grad ually reserving for the last those mentioned previously as the most common offenders Should symptoms recur suspicion should be di rected toward foods added during the *preceding two days* and particularly toward foods added during the preceding *24 hours*

FOOD DIARY—Obviously careful records of the diet must be made to ascertain what foods were ingested within the period im mediately preceding the development of symptoms Accordingly the patient should record each day *every* substance eaten at breakfast lunch dinner and between meals noting at the end of each day s entry the occurrence the *exact* time and the severity of symptoms By study of such data the physician may be able to establish a relation ship between the ingestion of a food and the occurrence of allergic manifestations

ELIMINATION DIETS—The same trial and error principle is in volved in all dietary restrictions and food diaries and forms the basis of the so-called elimination diets These are often employed as diag nostic aids in cases of food allergy when the clinical history and skin tests with food extracts have proved unavailing

Under this regime the patient is required to eat *nothing between meals* and to select all of his meals—breakfast, lunch, dinner—from a restricted list consisting of the following foods one meat (lamb) three fruits (lemons grapefruit, pears) five vegetables (lettuce, chard spinach carrot, sweet potato) and two starches

TABLE 9—ELIMINATION DIETS (ROWE)

	DIET 1	DIET 2	DIET 3
Starches	Rice	Rye	White potato
	Tapioca	Corn	Tapioca
Vegetables	Lettuce	Beets	Tomato
	Chard	Squash	Carrots
	Spinach	Asparagus	Lima and
	Carrot	Artichoke	string beans
	Sweet potato		Peas
Meats	Lamb	Chicken	Beef
		Bacon	Bacon
Fruit	Lemon	Pineapple	Lemon
	Grapefruit	Peach	Grapefruit
	Pears	Apricot	Peach
		Prune	Apricot
Sugars	Cane sugar	Cane sugar	Cane sugar
	Maple syrup	Corn syrup	Maple syrup
Miscellaneous	Sesame oil	Sesame oil	Sesame oil
	Gelatine	Mazola oil	Soy oil
	Salt	Gelatine	Gelatine
		Salt	Salt

From Row A. H *El minat n Diets d th Pat t' Allerg es* (Philad lph a Lea & Feb ge 1941)

(tapioca, rice rice bread) (Diet 1 Rowe) There is no limit placed on the *amount* of the permitted foods All other items of diet even of apparent unimportance are *completely and absolutely banned* There must be no lapses from the diet.

When symptom free the patient is permitted to add other foods *singly a two day period occurring before each new addition* If the restricted diet is unavailing in that there is no lessening or freedom from symptoms at the end of two weeks a similarly restricted but entirely different diet is substituted consisting of chicken bacon pineapple peach apple apricot prune beets squash asparagus artichokes corn or rye bread (Diet 2 Rowe)

SOME DIFFICULTIES IN EVALUATING ALLERGENIC EFFECTS OF FOODS —It is to be remembered that foods today are virtually always contaminated with traces of other foods and other added substances Thus no diary or elimination method will be able to take into account the minute exposures to the mixed in milk or eggs or wheat or spices or coloring materials or preservatives or antimolds or metallic salts or adjuvants such as vitamins some of which are unconsciously ingested with every meal and with every drink or morsel A food diary can be expected to record only the *conscious massive exposures* Therefore in patients whose symptoms are caused by minimal untraceable exposures to ingested allergens the food diary and other elimination methods will be valueless Fortunately not all patients are so hypersensitive that they react to traces of contaminants and adjuvants In fact the opposite is sometimes true and evaluation of food effects is difficult because small amounts are tolerated and only *massive* or *continued* exposures bring on untoward effects In attempting to correlate symptoms with exposures to food allergens it must also be remembered that reactions to offending foods may sometimes appear immediately whereas in other instances reactions may be delayed for as long as 24–48 hours or more after ingestion

An occasional patient will tolerate a food at one time but not at another These irregularities in tolerance render the classification of such cases most difficult The variations of response are often inexplicable but sometimes can be traced to variations in the food itself —variations in fruits and vegetables grown at different times or in different localities variations in milk or eggs or meat due to different feeding of poultry and animals variations of composition due to aging transportation sterilization cooking or other manner of preparation Another serious difficulty may be presented by the fact that some patients react to foods only when their ingestion coincides with other additive or synergistic influences (coincidental exposures to other foods drugs or inhalants coincidental infections or emotional disturbances)

In numerous cases for results of diets to be valid the eliminations must be complete yet to follow absolute elimination diets for several weeks to months is a practical impossibility for most adult ambulatory patients It requires not only an exceptional exercise of will but also an interruption of normal life a disruption of home social and business routines which is more often than not beyond the capacity of the average patient.

Owing to the difficulty of conscientious execution information obtained from the use of elimination diets will often be misleading Another drawback is that highly restrictive diets often are inadequate for protein vitamin and other nutritional requirements The patient must be closely supervised and must not be permitted to continue indefinitely on his limited menu. He must understand that the narrow choice of foods is for *diagnostic purposes only* and that once the offending foods are identified, the diet should be enlarged as rapidly as possible

Fortunately it is seldom that more than one or two foods such as milk, egg or wheat, are found to be harmful to any one patient. The person allergic to egg and poultry can usually tolerate fish and animal proteins the patient sensitive to legumes nuts and seeds is generally not disturbed by other vegetable foods Few patients indeed are clinically allergic to a wide variety of unrelated foods

Restrictive diets must be used with caution, if at all, in the under nourished. They are usually contraindicated when they conflict with diets used in diabetes nephritis and intestinal ailments

It is our conviction that in general, entirely too much importance is assigned to foods as allergic excitants Too many diagnoses of food allergy are made on the basis of unsubstantiated statements of the patient or unverified impressions of the physician. For example flatulence or deranged digestion may be ascribed, especially in the asthmatic, to food allergy when the actual cause is fatigue or mechanical pressure of the stomach against the diaphragm.

The presence of a food allergy cannot be said to have been proved regardless of findings by history or skin test unless the allergic

symptoms can be deliberately produced on ingestion of the suspected food substance

There are other types of food sensitization which cannot be discovered by dietary restrictions Chief among these are dermatoses caused by external contact with such vegetables as carrots beets spinach celery such fruits as orange banana peach or such meats as beef pork Respiratory forms of allergy due not to ingestion but to inhalation of dusts or particles of certain foods such as nuts wheat and coffee cannot usually be identified by dietary measures but are as a rule diagnosed by skin testing with extracts of these substances plus clinical elimination of the environmental sources

TESTS WITH DRUGS

This procedure is one of the most important in the search for allergens which elicit a great variety of diseases but *which cannot be discovered by skin tests* Many diseases of obscure causation ranging from urticarias to pemphigoid eruptions from purpuras to blood dyscrasias from cardiovascular diseases to liver disease from psychic disturbances to kidney damage from pruritus to febrile exanthems etc have in numerous instances been proved to be elicited by exposure to drugs

It is therefore an absolute requirement that not only every case presenting a picture *known* to have been occasioned by a drug allergy but also *every condition* of unknown causation be investigated by means of the avoidance of all possibly offending drugs In his search for potential causes the physician is guided by his ability to recognize the clinical changes most often caused by particular drugs as well as by his knowledge of notorious drug offenders by his information on when how and in what protean forms allergenic drugs are encountered by his skill and everlasting patience in extracting the history of drug exposures and by his detective powers in tracking down the drug suspects and clinching the evidence

The further details of this most important form of trial and error approach are discussed in the section on drug eruptions

CLINICAL TESTS WITH ECZEMATOGENIC ALLERGENS

Although the skin test (patch test) is most often of value in this form of allergy here too the final court must be the observation of results of avoidance and if necessary of re-exposure The many approaches to the selection of suspects and the methodical steps which must sometimes be taken to ascertain which allergens should be avoided in a given case are presented in the section on eczematous contact type allergic dermatitis

Chapter Two

COMMON TECHNICS

Prophylactic and Therapeutic Procedures

Marion B Sulzberger W C Spain and Rudolf L Baer

ONCE THE ALLERGEN or allergens eliciting reactions in a particular case have been discovered the prophylactic and therapeutic proce dures include *nonspecific measures* plus *specific immunologic forms of therapy* Although the former are often of decisive value only the latter fall within the scope of the present text

The available *specific immunologic* forms of prophylaxis and therapy are of considerable variety The appropriate measures depend on the category of allergic disease the types of allergens con cerned the clinical findings and many other features of the individual case Just as in immunologic diagnosis and in the search for elicit ing allergens success in immunologic treatment and prevention depends largely on the selection of those procedures which fit the case

The specific immunologic forms of prevention and treatment may be divided into two large groups

1 Avoidance of offending allergens
2 Immunization or hyposensitization through administration of offending allergens

Avoidance of Allergens

In the great majority of allergic diseases this is not only the best but often the only available specific measure As knowledge progresses it is certain that specific hyposensitizing and immunizing procedures will become of practicable value in more and more allergic conditions

Today despite the manifest success of specific hyposensitization in particular entities or cases most human allergies are best fore stalled or managed by *avoidance* of the offending exposures There are notable exceptions to this rule such as the specific hyposensitiza tion measures successfully practiced in hay fever and in certain types of asthma. But even in these conditions avoidance although only partial is desirable Certain cases of contact type eczematous derma titis from plant oils may also belong to the exceptions in which hyposensitizing measures have some success The details of the appli cable specific measures of hyposensitization or immunization are discussed under the individual entities

AVOIDANCE OF FOODS

Here the patient is instructed and helped to avoid the offending food allergens The measures used follow those described for avoid ance of foods *for diagnosis or discovery of eliciting* allergens (p 59) The difficulties encountered are also similar to those of diagnostic diets but are sometimes less for the elimination of a food need not always be complete to achieve significant reduction of symptoms On the other hand the difficulties are augmented by the fact that prophylactic and therapeutic diets must be continued longer than diagnostic ones Some patients must avoid the offending foods com pletely *and for good Many others get over their allergies to food* and may resume eating the previous offenders This is particularly true in the first and second age decades And as stated there are patients who may partake of a food occasionally or in small quan

tities without suffering whereas larger quantities or cumulative exposures cause discomfort or disease

The detailed directions for the relevant dietary eliminations are set forth on pages 59 63 and in the chapters on particular disease entities

AVOIDANCE OF DRUGS

Despite the bright promise of certain investigative studies *there is as yet no practicable way of hyposensitizing to most drugs Drug avoidance therefore is the only available measure of prophylaxis and therapy*

The dermatologic reactions to drugs were prominent among the earliest recognized allergic reactions to medicaments and until recently the technics for avoiding exposure to drugs were almost exclusively the province and interest of the dermatologist But with the introduction of modern chemotherapeutic and antibiotic agents—notably the sulfonamides and penicillin—the high incidence of drug reactions and the almost limitless diversity of their manifestations began to receive more general recognition It may be said that at present the technics of drug avoidance have become a therapeutic and prophylactic must for all practitioners Every physician should be acquainted with the drugs which have caused reactions the form of reaction each is most likely to elicit where and in what guises the notoriously allergenic drugs may be encountered and how to help the patient avoid both the manifest and occult exposures

This is a task of great magnitude one which cannot be fulfilled without the devotion of much time and attention. Drug avoidance is rendered particularly difficult today owing to the many *hidden* sources of drug exposure in pharmaceutical products in proprietary remedies (often in completely described on labels and in literature) in foods toilet articles cosmetics in occupational exposures and even in clothing and household articles It would require a book thicker than this one simply to list the commonly encountered items which contain *allergenically significant* quantities of such drugs as salicylates quinolins iodides bromides

phenolphthalein, phthalates benzoates barbiturates formalin sulfon amides mercurials and arsenicals and their derivatives to name but a few of the more frequent offenders.

Another difficulty lies in the fact that, like reactions to foods reactions to drugs do not necessarily or regularly follow each ex posure Temporary or permanent acquired or spontaneous hyposensitizations increased tolerance adjuvant or synergistic factors cumulative effects and quantitative considerations will all be found to influence the responses to drugs

The manner in which some of the difficulties may be overcome and the methods of drug avoidance are discussed in the pertinent sections (drug eruptions asthma urticaria)

AVOIDANCE OF INHALANT ALLERGENS

The so-called inhalant allergens are generally derived from biologic products and tend to cause principally respiratory reactions However they do on occasion elicit skin reactions either by absorption and *hematogenous distribution to the cutaneous shock tissues* or by external exposure and *percutaneous (transepidermal) penetration* to the vascular structures of the skin This type of reaction occurs mainly in some urticarias and in some atopic dermatoses and somewhat more commonly in infants and children than in adults (Such reactions must not be confused with the usual contact type allergic eczematous dermatitis commonly due to nonproteins and only rarely due to skin contact with and transepidermal penetration of *protein allergens*)

The avoidance of inhalant allergens includes avoidance not only of all air borne allergens pollens dusts etc derived from a variety of sources but also on occasion of external skin contact with wool silk cotton feathers danders etc In many cases of allergy of the eyes or respiratory organs due to inhalants (hay fever certain types of asthma) specific hyposensitization is of great value In other respiratory allergies hyposensitization is of little or no effect and avoidance plus nonspecific measures are the only available proce

dures And in dermatologic reactions to inhalant allergens—whether from hematogenous distribution or percutaneous penetration on external contact—we believe that *hyposensitization has not yet proved itself to be of regular or practical value and that avoidance or reduction of exposures is the sole specific form of management*

AIR BORNE ALLERGENS —Pollens dusts powders danders and lints are the inhalant substances most important as allergens largely because they are transported through the air With the exception of pollens these allergens usually emanate from sources near the patient The *home, particularly the bedroom is the most important place of origin of air borne allergens* Whenever feasible the following procedure should be used to reduce exposure in cases of proved or presumptive allergy to inhalants

The Allergen-Poor Bedroom

1 Of course the best and simplest method of pollen avoidance is to reside in a region free of the disturbing pollens When this is not practicable reduce exposure to pollen by installing in one of the bedroom windows an efficient air-conditioner which filters but does not chill the air All doors and all other windows of the room must be kept closed

2 The room should be completely emptied just as if you were moving out Closets should be emptied and cleaned if at all possible contents should be stored elsewhere and the closets sealed The woodwork and floor should be thoroughly cleaned and scrubbed to remove all traces of dust Floor or linoleum should be oiled or waxed linoleum, if used should be cemented to the floor (If flax sensitive do not use linoleum use wooden floor instead covered with paint not containing linseed.)

3 The room should contain only one bed preferably a simple iron bed Bed and spring should be scrubbed outside the room. If box springs are used they should be covered with dustproof casing

The mattress and pillow should preferably be made either of latex rubber or fiberglass or of pure cleaned hair from the mane or tail of the horse which contains keratin but no dander Horsehair mattresses

are particularly preferred because they can be routinely cleaned and renovated If this is not feasible the mattress and pillow should be covered with dustproof casing of rubber or plastic treated fabric After enclosing the pillow or mattress in the casing seal the end with a wide strip of adhesive tape Box springs must be treated in a like manner

Use only washable materials on the bed Sheets and blankets should be laundered at frequent intervals No mattress pad, fuzzy wool blankets feather or wool stuffed comforters should be used Woolen blankets which have been washed several times may be used Wool fabrics are permissible except for loosely woven materials such as Shetland wool. Knitting wool must be avoided. If a second bed must be kept in the room, it must be prepared in the same manner as the patient s bed

4 A wooden or metal chair which has been scrubbed should be used The room should contain a minimum of furniture and furnishings and *no* upholstered furniture

5 If essential, rag rugs may be used on the floor and plain light curtains on the windows both must be washed once weekly

6 If there is a furnace or hot air outlet in the room a dust filter made of several layers of cheesecloth or other adequate material should be installed this filter should be changed frequently Holes and cracks in the floor around heating or other pipes must be sealed For this purpose adhesive tape is useful, although scotch tape is adequate for some cracks

7 If the patient is a child only washable toys of wood rubber metal or plastic should be permitted in the room.

8 The room must be cleaned daily with a damp cloth or oil mop Once a week the room, including the floor furniture tops of doors window frames sills etc., should be given a thorough and complete cleaning

9 The room should be thoroughly aired daily and the doors and windows then closed until the patient is ready to occupy it The room should be used for sleeping only Dressing and undressing should be done and all clothing kept, in another room Avoid garments and furnishings lined or trimmed with rabbit hair such as inexpensive fur coats bedroom garments bedroom slippers gloves and galoshes

CONTROL OF ENVIRONMENTAL INHALANT ALLERGENS —En vironmental control consists in making the patient s surroundings as free as possible from *dust of all kinds* and from other notorious inhalant allergens The important directions for such control are

1 Air all rooms thoroughly if possible filter or wash incoming air through air filters or an air conditioning set

2 Keep down the dust throughout the entire house Go over all floors and furniture with a vacuum cleaner at frequent intervals —once a day if possible

3 All other dusting should be done with a damp or oiled cloth to avoid raising dust In extreme cases oil spraying of the entire room and furnishings mav be carried out in a manner identical to that used in combating respiratory and air borne infections Clean ing and dusting should be done while the patient is away from the house If the patient himself has to do the cleaning he must wear a dust mask

4 Have as little as possible dust forming and dust holding furniture and furnishings in the home (no upholstered furniture carpets and drapes!)

5 Keep the patient away from objects covered with dust such as books boxes shelves cupboards closets and attics where articles have been stored

6 Steam or hot water heat is preferable to hot air heat

7 Avoid if possible the use of insecticides if insecticide spray is necessary use Kilit

8 Avoid odoriferous substances such as perfumes camphor moth balls or flakes tar paper wet paint gasoline smokes

9 Keep no flowers or plants in the house

10 Be sure that no member of the household uses cosmetics containing orris root (in face foot dental and talcum powders), rice powder Karaya gum

11 Reduce sources of feathers furs animal hairs wool and silk both in room furnishings and toys

12 Keep away all animals with fur or feathers

AVOIDANCE OF CONTACT TYPE ECZEMATOGENIC ALLERGENS

In a *few* forms of contact type allergic eczematous dermatitis prophylaxis through administration of ascending doses of the appropriate allergen appears to be of some value Poison ivy dermatitis may be cited as an example In the *vast majority of cases* however the sole specific measure is the avoidance of or reduction of exposure to the eliciting eczematogenic allergens In many of these cases the situation is simple and clearcut exposures to a certain article are always followed by eczematous dermatitis discarding or avoiding that article results in cure But in other instances the influences of additive and synergistic factors the spontaneous fluctuations of degree of sensitivity and many other circumstances complicate the issue

Some patients tolerate exposures at one time but not at others some will react to a single exposure to infinitesimal traces others only to massive or to repeated exposures some will react strongly at certain skin sites but less so or not at all at others In addition many show evidence of *acquired clinical* hypo or desensitization after single or repeated exposures to the specific allergen as well as evidence of periods of *local* or general *refractoriness* to reaction after clinical eruptions

The erratic spontaneous or acquired fluctuations in level of sensitivity as well as the ever present and multitudinous opportunities for occult exposures to eczematogenic allergens are analogous to those mentioned under avoidance of foods and drugs Such complex factors may render difficult both the carrying out of allergen avoidance and the evaluation of its effects Nevertheless there is probably *no allergic disease in which the search for eliciting allergens the tracing down of all manifest and occult sources and their meticulous avoidance yields more satisfactory results than in cases of acute eczematous contact type dermatitis*

The measures and means for discovering and avoiding exposures are varied and depend on the nature of the eczematogenic allergen

concerned the natural or artificial products in which it is encountered and many other factors Although it is impossible to give detailed instructions for avoiding each of the almost numberless eczematogenic allergens some directions are set forth in the section on eczematous contact type allergic dermatitis in Chapter 6

Active Specific Hyposensitization or Immunization

In many pathologic conditions natural exposures lead to immunity desensitization or hyposensitization It is now established that adequate exposure regularly leads to immunity of considerable duration in diphtheria smallpox various other infectious diseases and many common infectious exanthems There is no such unequivocal evidence of naturally acquired immunity or of increased clinical resistance in other allergic conditions such as contact type eczematous dermatitis drug eruptions and food and inhalant allergies Nevertheless it is certain that in allergic occupational dermatoses and allergic plant dermatoses as well as during the course of administration of certain allergenic drugs or during repeated more or less continuous exposures to certain food or inhalant allergens some individuals may at least temporarily acquire greater clinical resistance or clinical immunity

In addition to being supported by considerable experimental evidence this conclusion is confirmed by clinical observations of cases of specifically acquired hardening or diminution of clinical hypersensitivity in industrial and in plant dermatitis by evidence of loss or reduction of sensitivity to such drugs as arsenicals iodides sulfonamides and penicillin *even during their continued administration*, and by prevention of sensitization or reduction of sensitivity during continued exposure to ingested or to inhaled allergens In many such cases any significant *interruption* in the specific exposures may be followed by *renewed elevation* in the level of sensitivity and by clinical reactions on resumption of exposure

Indeed the generalization may be warranted that continued more or less *uninterrupted exposures to certain allergens* (seasonal pollens poison ivy strawberries shellfish and other seasonal foods etc) *often tend to keep down the level of allergic sensitivity whereas interrupted or sporadic exposures are rather inclined to permit sensitizations to reach their highest levels* It is therefore understandable that deliberate measured therapeutic or prophylactic administrations of the infecting agents or their derivatives are often eminently successful in producing immunity in diseases in which natural exposures are regularly followed by significant periods of immunity And it is also comprehensible that deliberate administrations of allergen are not regularly successful in most forms of human allergy but that when given so as to modify the quantity route chronologic spacing and intermittence of the natural exposures these specific administrations may in some conditions succeed in increasing clinical tolerance

The technics of such deliberate specific immunizing or hyposensitizing measures are described in the chapters dealing with the particular entities

ROUTES AND TECHNICS OF ADMINISTRATION —The routes by which specific hyposensitizing or immunizing agents can be administered are as varied as those for the administration of drugs in general Some routes such as intracutaneous inoculation intracutaneous subcutaneous and intramuscular injection and oral administration are commonly employed and have been well studied *Other routes such as intravenous injection inhalation and external application to the skin s surface may well deserve further exploration* in relation to particular allergens and diseases but are not today in general practical use

INTRACUTANEOUS INOCULATION

This procedure is usually employed with attenuated *living* agents of disease such as vaccinia virus The technic is well known to all physicians The method usually consists of inoculation on multiple punctures or on scratches so superficial as not to draw blood (p 158)

Occasionally intracutaneous injection of the material has been employed

The principal precautions are those designed to prevent inadvertent dissemination of the virus to objects to other persons or to parts of the patient in which reactions would be undesirable or disastrous Thus *no person with itching or excoriated skin or with active open lesions should be vaccinated unless the procedure is of absolute and vital necessity* Precautions must always be adequate to forestall accidental inoculation of the eye or of multiple skin sites Dermatologists and others who treat skin diseases must protect their other patients by taking special precautions for cleanliness of person and equipment and for disposal of virus contaminated instruments and objects

INTRACUTANEOUS OR INTRADERMAL INJECTIONS

These prophylactic or therapeutic injections are given in the same sites and with the same technic described under intracutaneous injections for diagnosis (p 39) The usual amount is 0 1 cc of fluid containing the appropriate dose of vaccine allergen or toxin Quite often multiple injections of 0 1 cc each can be given in several sites at one time

There is evidence that *in some conditions intracutaneous injections have greater immunologic effect than subcutaneous or intramuscular injections* of equivalent amounts of allergenic materials This fact is put to practical use in certain immunizing procedures (e g typhoid vaccination)

Before starting injections the physician must have ascertained not only the agents to be used but the dosage appropriate to the patient s level of sensitivity Otherwise overdosage and severe damage may occur

The dangers and precautions in intracutaneous prophylactic and therapeutic injections are analogous to those described under the directions for intracutaneous skin testing (p 41) *Constitutional reactions are even more likely* to result from *prophylactic and therapeutic injections* than from the usually smaller diagnostic injections

and *all preparations must have been made for the avoidance and management of reactions* (pp 91 ff)

SUBCUTANEOUS OR HYPODERMIC INJECTIONS

Although this technic is also too well known to require lengthy description here a few special directions may not be out of place for this most commonly employed of all immunologic procedures Before injecting the physician must have determined not only which immunizing or hyposensitizing agents should be used but also the degree of the patient s sensitivity The material to be injected must then be given in appropriate form and concentration If this is not done overdosage and serious consequences will often result And of course the usual preparations must have been made for prevention and management of constitutional and other untoward reactions

CHOICE OF INJECTION SITE

The site of choice is the lateral aspect of the upper arm or the anterior or lateral aspect of the thigh

TECHNIC OF INJECTION

The skin on the arm or thigh should be grasped in a fold held between the thumb and forefinger of the left hand[1] and slightly lifted above the plane of the underlying muscle so that the point of the needle may penetrate through the skin and not into the muscle The fluid should enter into the space provided by the lifting of the skin for any deposit made within the skin or muscle may cause unnecessary pain In patients with urticarial skin sensitivity the unavoidable cutaneous deposit of traces of the material may lead to a growing wheal

Some patients will be alarmed or discomfited at the prick of the needle Most persons are not accustomed to the slight pain of hypodermic injection but have experienced and discounted the discomfort from a pinching of the skin If at the moment of plunging the needle

[1] Read right hand for left handed person

into the skin some pressure is exerted by the left thumb and fore finger on the fold of tightly held skin the diffuse slight pain of the pinching will distract the patient s attention to this area and the dis comfort of the needle thrust will be lessened

A 26 gage needle ½ or ¾ in long with point kept *well sharp ened,* should be used The syringe with needle attached both sterile should be held with the right[2] thumb and middle finger somewhat as though it were a pen but with the right[2] index finger free to exert pressure on the head of the plunger the moment the needle has been inserted

CONTRAINDICATIONS AND DANGERS

Since the accidental administration of allergenic material into a vein will in many cases cause sudden and often severe general re actions various procedures have been offered as safety measures

1 It is occasionally suggested that after insertion of the needle and before injection of the syringe contents the plunger be slightly withdrawn in the barrel to assure the operator that no blood can be aspirated and that the point of the needle is not resting within a blood vessel Such a procedure is not only cumbersome but unre liable since general reactions from intravenous injection have often occurred despite this precaution

2 Another suggested precaution is the use of the cuff of a blood pressure apparatus The cuff is placed around the extremity proximal to the site of the anticipated injection and inflated to a pressure just above the venous pressure of the patient to retard the flow of any extract injected intravenously by accident the pressure is removed subsequent to the injection This procedure invites apprehension in the patient and is time consuming it is impracticable and is of use in only a small percentage of cases for the general reaction often appears 10–20 minutes after the injection

3 The admixture of a small amount 0 1 cc or 0 2 cc of a 1 1 000 epinephrine solution in the syringe has been advocated This

[2]Read left for left handed person

tends only to obscure the picture and does not prevent severe constitutional reactions

We find that the *most sensible and practicable methods of avoiding general reactions* are

1 Scrupulous care and judgment in selecting and using the proper dose

2 Utmost care in obtaining properly standardized, reliable and fresh extracts

LOCAL RESPONSE

In most cases with an urticarial form of sensitivity within *1–10* minutes following *hypodermic* injection itching erythema swelling and a single wheal or a cluster of small hives appear at the site of injection

The *wheal* may be only 0 5–1 cm in diameter however in severe local reactions it may be 6–12 cm in diameter The larger local reactions may persist for relatively long periods sometimes over 24 hours The size and type of the local reaction should always be noted by the physician and at the subsequent visit the patient should be questioned about its extension and persistence *Such data provide a most helpful guide to the correct dose for the next injection* Whenever a large and persistent reaction develops at the site of injection usually the subsequent injection should be a *reduction* occasionally a *repetition* of the previous dose and *never an increase* in amount

SIMULTANEOUS ADMINISTRATION OF DIFFERENT ALLERGENS

Thanks to the considerable specificity of the reaction invoked by the administration of an allergen a patient may be receiving one allergenic extract to which he is sensitive to the limit of his tolerance and yet accept simultaneous injections of one or more other types of allergenic extracts to which he is equally sensitive This holds true provided there is no close immunologic relationship between the allergens involved

For example a patient may receive simultaneously without incident large injections of *birch* and *ragweed* pollen extracts at the time he is receiving his limit of *timothy* grass pollen extract There might be a disaster however if large doses of *orchard* and *sweet vernal grass* pollen extracts were given at the same time as full doses of pollen extract of *timothy*—all closely related species

Even with completely unrelated and dissimilar extracts it should be the rule to *avoid giving more than three* allergens during the same period of treatment

The *effects of simultaneous administration of different allergens are not yet entirely understood There is sometimes a synergistic or potentiating action, leading to greater immunologic effects, conversely, there may sometimes be reciprocal inhibitory influences, resulting in reduction or inhibition of the expected immunologic effectiveness*

INTRAMUSCULAR INJECTIONS

This is the method most used for administration of desensitizing or immunizing materials in *oily solution*, in *emulsion* or in *suspension* The technic need not be described since it is *identical* with that regularly used by physicians for intramuscular injections of other agents (bismuth in oil hormones in oil etc) The preferred site is the upper outer quadrant of the buttock for the average adult the needle should be about 22 gage and about 2½ in long

CONTRAINDICATIONS PRECAUTIONS AND DANGERS

Of course the usual strict precautions must be observed to prevent *intravenous* injection or *intra arterial* injection and the consequent often serious arterial embolism and peripheral infarction (embolia cutis medicamentosa) Statistics indicate that even with the best available technics and all precautions *arterial embolism* may result about once in each 10 000 intramuscular injections (The severe reactions and necrotic infarcts which result are often mistaken for Arthus like local allergic reactions and may have been erroneously published as such)

Although the general precautions and hazards are those of all forms of intramuscular injections when *eczematogenic* allergens are administered by this route special steps must be taken to prevent *back leakage* or contamination of the skin surface and the resulting sometimes severe and spreading dermatitis These steps include

1 The insertion of a needle which is both clean and *empty* and without previous contamination by allergens

2 The pulling down hard on the buttock with the hand not holding the needle This displaces the superficial cutaneous and fatty layers so that when they slide back to normal position the needle track between allergen deposit and skin is obliterated

3 The inclusion of a small bubble of air in the syringe *behind* the column of fluid and the injection of this air into the buttock to clear the needle before its withdrawal

4 The rapid withdrawal of the needle and immediate pressure with sterile sponge to the site of needle puncture This pressure is maintained sufficiently long to stop all back leakage

5 The sponging of the skin surrounding the injection site with oxidizing substances (hydrogen peroxide potassium permanganate in 1 1 000 solution chlorinating ointments etc) after intramuscular injections of contact type allergens susceptible to destruction with oxidizing or chlorinating agents

6 Meticulous attention to prevent traces of allergen solution from contaminating any objects instruments hands clothing etc which might touch the patient s skin

Even with these precautions in an occasional patient dermatitis will develop around the injection site or even in distant areas

Unless there is inadvertent intravenous administration the intra muscular injection of allergens in oil or in suspension does not usually carry with it any significant danger of constitutional reac tions (Intravenous injection of oils may produce pulmonary emboli The condition of the patient may appear grave but there is usually prompt and full recovery)

Local reactions of varying degrees even some with *severe swelling* or Arthus like necrosis sometimes with *fever* and other systemic derangements occasionally will occur in strongly hypersensitive subjects or will result from overdosage

Another complication of intramuscular injection of allergen is the *focal flare up* a recurrence or exacerbation of old lesions or the spread and involvement of new areas by the pathologic skin condition under treatment This will occur with intramuscular as readily as with other forms of administration Unless the indications are imperative the dictum that no injections of allergens should be given during acute active stages applies here as strongly as it does to administration by any other route Indeed there are also indications that suspension in oil and intramuscular injection often provides a depot of slowly absorbed material which tends to increase or potentiate the immunologic effects of the allergenic substance

ORAL ADMINISTRATION

There is increasing evidence that in certain forms of immunizing or hyposensitizing procedures the results of oral administration may compare favorably with those of other routes of administration Prophylaxis or treatment by the ingestion of allergenic substances naturally possesses some attractive practical advantages However the proportion of the administered dose actually absorbed is difficult to ascertain or to regulate and the precision of dosage cannot be expected to approximate that attainable through the injection of allergen

The present use of oral hyposensitizing or immunizing procedures is limited Their greatest field of usefulness today is in administration of *plant oils* for prophylaxis of *plant dermatitis* (poison ivy etc) This method appears to be useful in certain cases and certainly achieves results as good as or better than the results of intramuscular injections Unfortunately many of the untoward effects are difficult or impossible to obviate (p 305)

CONTRAINDICATIONS PRECAUTIONS AND DANGERS

Among the untoward reactions from oral administration of plant allergens are

1 Flare ups at old sites and/or spread of the dermatitis to new areas (especially vesicular eruptions of the hands)

2 Pruritus of the anus vulva and penis sometimes with accom panying dermatitis

3 Nausea vomiting and gastrointestinal upsets

4 Cheilitis and occasionally stomatitis glossitis pharyngitis

These manifestations are common and are disagreeable although rarely dangerous The untoward reactions together with the present necessity for long continued administration of gradually ascending doses and the more or less *temporary* and *incomplete* protection usually achieved indicate that improvement of the method is still needed. We are convinced that oral hyposensitization at present *must be reserved for carefully selected cases and for patients who will exactly carry out instructions and be available for the necessary control and observations*

The effectiveness of oral administration of most immunizing or hyposensitizing agents other than plant or vegetable oils is still a controversial issue Preparations for oral use are discussed in the sec tions dealing with the particular entities whenever supporting evi dence appears sufficient to warrant clinical trial

EXTERNAL APPLICATIONS OF ALLERGENS TO THE SKIN

The external application of allergens to grossly normal skin has universal recognition as a useful *diagnostic* measure (e g patch tests and other applications in allergic contact type dermatitis) But ex ternal applications *for the purpose of hyposensitizing or immunizing* have had little use and have received but little study There have been some reports on successful immunization by inunction of toxin or toxoid in diphtheria and in certain other infections and there are isolated reports on successful hyposensitization by external applica tion in contact dermatitis from plants (Maisel)

Based on both older and more recent observations in the laboratory as well as on the commonly observed hyposensitization or hardening through external clinical exposures in certain occupational eruptions *it is our belief that hyposensitization by external applications of graded dilutions of eczematogenic allergens deserves more study in contact type eczematous dermatitis*

OTHER ROUTES OF ADMINISTRATION

Respiratory intraocular intranasal buccal lingual rectal and other routes of administration of immunologic agents have received little attention and study Regarding their possible practical usefulness we know virtually nothing

Passive Immunization—Prevention and Management of Serum Reactions

Foreign or heterologous serums which are those derived from species other than man as well as serums and other biologic products of human origin (homologous) are often administered to supply various types of antibodies Moreover other biologic products—plasma serums whole blood and organ extracts—are administered for various diagnostic therapeutic and prophylactic purposes Among these biologic agents the *heterologous products are most likely to be antigenic* and to cause *sensitizations and allergic reactions* However even homologous products once removed from the body become sufficiently denatured and foreign to be capable of some antigenic action. In addition there may be certain natural differences between the human donor and his products and the human recipient which sometimes lead to incompatibilities resulting in severe reaction (for incompatibility of blood groups and Rh factors see Chapter 4)

The methods of administering these biologic products are not only well known to the practicing physician but are well described both in the general medical literature and in the special instructions

usually accompanying the products The following discussion is therefore confined to the mechanisms the prophylaxis and the management of the various *forms of reactions* which foreign serums and other biologic products may produce

REACTIONS TO HETEROLOGOUS PRODUCTS

1 *Severe explosive and sometimes fatal systemic or general reactions* can occur even in persons who have apparently had *no* previous exposure to the particular foreign serum Fortunately these severe reactions are rare They occur *almost exclusively* in *atopic individuals* Therefore before administering the serum of a foreign species the physician *must* investigate most scrupulously for manifestations of *atopy* (hay fever asthma, atopic dermatoses such as infantile eczema neurodermatitis disseminata flexural eruptions prurigos etc) in patient and family It is probable these extremely hypersensitive *atopic* individuals are *not born* with specific foreign serum sensitivity but have *acquired* it usually through minute occult exposures to the serum antigens or to immunologically related agents (e g exposure to horse dander or horse meat leading to sensitivity to horse serum) If atopy is present or strongly suspected foreign serum should *not* be given except in cases of urgent necessity and then only by beginning with very small amounts after all precautions ophthalmic tests and other tests have been meticulously carried out (p 93)

The symptomatology and management of severe systemic reactions are described under general or constitutional reactions (p 90)

2 *Sensitizations of the usual foreign protein type* will of course occur in a considerable percentage of normal persons exposed to therapeutic or prophylactic doses of foreign serums These sensitizations and their results will last for an unpredictable time Hence emphasis is placed on the importance of questioning for previous foreign serum administrations and of performing proper tests before large amounts of therapeutic serum are injected (p 54) The types of reactions caused by readministration of foreign serum in the sensi

tized person range from severe explosive constitutional reactions to mild urticaria or itching in many instances there will be the cutane ous and general picture of *serum sickness* The prevention and man agement of these reactions are discussed on pages 91 ff

3 *Febrile reactions* after parenteral injections of almost any solu tion in relatively large volumes—say physiologic saline or dextrose solutions—have been found to be caused by minute amounts of sub stances derived from micro organisms and plants that grow in the solution or in some of its ingredients before sterilization (pyrogens)

The same type of febrile reaction will occur on administration of blood or serum if extreme precautions have not been taken in the collection and storage of the material and in regard to everything used in its preparation—for instance containers filters diluting fluids The handling of enormous amounts of blood plasma during the war provided most valuable experience in the prevention of this source of side reactions Biologic tests for the detection of pyrogen have been developed and in the United States have been made obligatory for every therapeutic serum sold after Mar 1 1946

4 *Serum Sickness* Late reactions i e those appearing five or more days after serotherapy are observed in the form of fever mor billiform scarlatiniform multiform erythematous urticarial or pur puric rashes pains and swelling of the joints general malaise etc This syndrome is called serum sickness or serum disease and usually occurs 6–14 days after the administration of a sensitizing dose of a foreign serum When the serum sickness is characteristic it is easily recognized But some serum reactions can be puzzling especially when they masquerade as *relapses of the infection* for which the serum had been given or when unusual symptoms such as neurologic changes and palsies occur in the serum treatment of tetanus or diphtheria

To understand the mechanism of serum sickness it is necessary to know that parenterally introduced serum remains in the body tissues and fluids for a considerable time Thus at the end of the incubation period of the sensitization, i e when antibodies against the foreign pro tein have reached a certain quantitative level the antigen is still present

in the body The reaction of this residual antigen with the newly formed antibodies is thought to be the cause of serum sickness

It has been suggested that serum sickness may occur even after in jection of human plasma. This appears to be entirely possible for it is well known that serum proteins carry individual antigenic characters However the important form is that commonly appearing after the in troduction of the serum of a different species In this form the antigenic ity is determined by those factors associated with species specificity In the past most cases of serum sickness have resulted from the admin istration of *antitoxic serums* derived from artificially immunized horses (tetanus and diphtheria antitoxins) Today the incidence of serum sickness can be greatly diminished by subjecting the antitoxic foreign serum to a *directed process of peptic digestion* In this process the pro teins are modified just enough to destroy most of the horse or other species specificity and the foreign protein antigenicity *without damage to the essential combining and neutralizing properties of the antitoxin* This procedure is called despeciation or modification of antitoxic serums It has been demonstrated both experimentally and clinically that modified antitoxins have lost most of their ability both to sensitize and to elicit reaction. Obviously the ensuing reduction in the incidence and severity of serum reactions represents a great advance

No method has yet been found to modify the specificity of *antibac terial* serums Unfortunately neither *rabbit* antibacterial antibodies nor *equine* antibacterial antibodies withstand the digestive process Thus no despeciated antibacterial serums are as yet available

Treatment of Serum Sickness—According to the predominating signs and symptoms both the topical and general treatment of serum sickness follow the treatment recommended in urticarial eruptions erythema multiforme purpuras etc Antipyretics are useful in com bating the fever However any drug must be used with circum spection since it too may act as an allergen and add to the already present troubles For acute stages and emergencies adrenalin ad ministration is indicated (p 92) Perhaps the most promising form of therapy is the administration of the new so-called antihistaminic agents (Pyribenzamine—Ciba and Benadryl—Parke Davis) From

150–300 mg is given by mouth over a 24 hour period in doses of 25 mg every 2–4 hours

Once the disease has been recognized the principal object of treat ment is to make the patient more comfortable Serum sickness is usually a harmless and self limited condition which cures itself within a few minutes to 18 days

THE GENERAL OR CONSTITUTIONAL REACTION

The so called general systemic or constitutional reaction occurs as a result of excessive allergenic exposure in patients with shock tissues capable of immediate or explosive allergic reactions (usually vascular shock tissue) This means that constitutional re actions will appear in atopic individuals and in persons with urti carial or other immediate forms of allergic response whenever the allergenic exposures exceed the patient s limit of tolerance

This can occur regardless of whether the allergen is a foreign serum a food an inhalant or some other immunologic agent The constitutional reaction can be the result of *clinical* exposures of *test ing* procedures or of *prophylactic* or *therapeutic administrations* Of course the limit of tolerance varies widely in different allergic and in different atopic individuals

Many of the directions mentioned in the sections on skin testing and in the sections on intracutaneous subcutaneous and other pro phylactic or therapeutic administrations are designed to obviate the serious complication of a general reaction Every physician who undertakes skin testing or immunologic prophylaxis and therapy must first be cognizant of the precautionary and other measures for recognizing preventing and managing constitutional reactions

SIGNS AND SYMPTOMS —Recognition of an imminent or devel oping general reaction is based on the following evidence

A *Early evidence* (almost immediately on giving the injection)

1 Itching of the palms

2 Flushing of the face neck upper chest

3 Mild, persistent clearing of throat
4 Hacking cough or persistent sneezing
5 Large urticarial wheal at site of injection

B *Subsequent evidence* (within 1–15 minutes)

1 Spread of the itching and erythema
2 Extensive urticaria (if injection has been given in the arm at first axillary and cervical then general especially of eyes and face)
3 Severe bronchial asthma and/or rhinitis conjunctivitis
4 Abdominal cramps and/or uterine cramps in women
5 Diarrhea
6 Vomiting

C. *Final evidence in severe cases*

1 General edema involving especially the eyelids lips tongue larynx and bronchial tree
2 Cyanosis
3 Shock, unconsciousness
4 Complete and permanent cessation of breathing (from edema of the larynx?)

General reactions often occur within a few seconds after administration of an overdose especially if the injection is accidentally given intravenously But it is important for the physician to realize that a constitutional reaction *may not start for as long as 60 minutes or more after an injection* For this reason no patient should be allowed to leave in less than an hour after an immunologic administration. As a rule the shorter the interval before onset of a general reaction, the more uncertain or disastrous the outcome

TREATMENT—When an immunologic test or treatment has been given and the imminence or the presence of a general reaction is recognized, a *tourniquet should immediately be applied to the extremity proximal to the site of the test or injection Epinephrine*

should be administered as soon as the tourniquet is in place and should of course be injected *proximal* to the tourniquet The *earlier* the epinephrine administration the surer the benefit. Depending on the severity of symptoms and the speed with which they appear as well as on the general state of the patient epinephrine 1 1 000 is given hypodermically in amounts of 0 5–1 cc (8–16 minims) re peated each 3–15 minutes if necessary In severe general reactions a total of 5 cc of epinephrine may be given without serious risk of permanent ill effect Patients in extremis may be given 1 cc or more of epinephrine 1 1 000 intravenously[3] using the 1 cc Luer testing syringe with 26 gage needle As ultimate measures intracardial in jections of adrenalin and massage electric or other direct stimulation of the heart have been used Strychnine camphor strophanthin in jectable digitalis products and amyl nitrite are usually of little avail Oxygen may be helpful but is seldom available in time

MEASURES EMPLOYED AGAINST GENERAL REACTION

Immediately on realization or strong suspicion

1 Tourniquet to extremity *proximal* to site of injection.
2 Epinephrine 1 1 000 1 cc. by hypodermic injection *proximal* to tourniquet repeat each 3–15 minutes if necessary
3 Epinephrine 1 1 000 1 cc or more intravenously for patients in extremis
4 Oxygen by inhalation if available

*Epinephrine should not be injected intravenously except in grave constitu tional reactions or in cases of severe intractable asthma In such emergencies 0 5–1 cc. aqueous 1 1 000 solution may be added to 50 cc. of concentrated (25–50 per cent) dextrose or glucose solution and administered slowly by the intravenous route Patients with chronic asthma who use frequent subcutaneous injections of epinephrine will testify that the occasional accidental delivery of the drug into the blood stream is usually followed by highly unpleasant effects Extreme palpitation pallor tachycardia vertigo prostration and exquisite pain in the frontal and temporal areas of the head are characteristic results

Whereas even the milder constitutional reactions demand imme diate treatment with quick acting drugs the oral use of such drugs as Pyribenzamine or Benadryl is contraindicated Instead subcutaneous injection of epinephrine should be instituted without delay

DRUGS USUALLY OF LITTLE VALUE IN GENERAL REACTIONS

Strychnine	Injectable digitalis
Camphor in oil	preparations
Strophanthin	Amyl nitrite

PREVENTION —Since constitutional reactions are caused by over whelming the allergic patient with the allergen to which he is sensi tive the most effective therapy is preventive The precautions to be observed have already been mentioned in the sections on skin testing prophylaxis and therapy For the sake of emphasis the more im portant will be repeated here

1 Before testing or treatment the physician must obtain a full history he must ascertain in advance and employ with particular respect those substances which are known or suspected to be capable of causing abrupt or severe reactions in the particular patient He must also use particular caution when testing or treating with aller gens notorious for causing general reactions

2 The physician must use every precaution to select the proper dilutions and amounts of allergens for testing and treatment

3 At every administration of allergen whether for test preven tion or treatment all specified prerequisites for obviating or man aging general reactions must be prepared and at hand

4 Whenever possible intracutaneous or subcutaneous injections should be given in the optimal sites namely the lateral aspect of upper arm and anterior aspect of thigh In these areas there is less chance of accidental injection into a blood vessel—an accident which

leads to the speediest and the most severe of general reactions Also the dissemination of antigen from these sites can be slowed by a proximally placed tourniquet

5 After each test or treatment the physician must keep the patient *under observation (and within easy access for an injection of* epinephrine) for at least 20 minutes the interval within which the most severe reactions occur The patient should not leave the premises for an hour

Chapter Three

IMMUNOLOGY OF INFECTIONS

Abram Kanof and Alfred J Weil

Introduction

THE FOLLOWING PAGES give in detail the immunologic procedures practicable in the office of the physician for the prevention diagnosis and treatment of most of the important infectious diseases of mankind Table 10 summarizes those active immunization procedures commonly employed in the prevention of infectious diseases

DEFINITIONS

For clarity the following short definitions of the terms used are given.

Exotoxin (= toxin) A specifically antigenic poison produced by certain micro-organisms which is characteristically diffused within the medium in which the organisms are grown rather than retained in the bacterial bodies

Toxin-antitoxin for immunization A mixture of toxin and its corresponding antitoxin. The poisonous effect of the toxin is neutralized by the antitoxin without impairing its antigenic properties Such mixtures have been used for active immunization particularly against diphtheria They are today largely superseded by toxoid

TABLE 10A.—ACCEPTED METHODS OF ACTIVE IMMUNIZATION PROCEDURES RECOMMENDED FOR ROUTINE USE IN CHILDREN

Disease	Indication	Material Used	Method and Dosage	Duration of Immunity	Reimmunization	Adverse Reactions	Comment
Diphtheria	*Routine practice at 9 mo*	Toxoid alum precipitated	*0.5 cc, 1 cc and 1 cc subcutaneously at 1 mo intervals*	5–6 yr	*1 cc on entering school*	Unusual in infancy, frequent in older children and adults	*Method for older children and adults p 116; often combined with tetanus, sometimes with pertussis immunization*
Pertussis	*Routine practice at 5 mo*	Vaccine 10,000, 15,000 or 20,000 million microorganisms per cc.	*1, 2 cc and 3 cc (15,000 million organisms per cc) subcutaneously at 1 mo intervals; ... ter als ... ars ... u th c ... centr t o*	4–6 yr	*2 cc (15,000 million per cc) at 3 yr and entering school*	Occasional moderate local, rarely febrile	*Combined immunization with tetanus and diphtheria often used but not universally accepted*
Scarlet fever	*1 In orphanages 2 Personnel in contagious disease hospitals 3 In hospitals or schools to terminate epidemics*	Scarlet fever toxin, preferably Veldee to	*650, 2,500, 10,000, 30,000 and 120,000 skin test doses subcutaneously at weekly intervals; Veldee toxin intracutaneously (p 150)*	Unknown	*No*	Many often severe	*Not generally recommended as public health measure or as routine practice; however, Veldee toxin and technic reduce reactions*

TABLE 10A —CONTINUED

D	I d l	M t l U d	M h d o d D og	D rot l Imm ty	R pe t Imm i s	Ad R i	Comm t
Sm llpo	1 Ro t e pr t c t 3–4 mo 2 O enters g ho l 3 In f e l pidem c 4 O nter g d m d	Cowpo rus cc ne	M lt pl pu t method	5 yr	As d t d	I freq nt	
T ta s	1 R ut pr c i e at 9 m 2 At a y age n per ons s bj t to in r liabl to l ta s je t n	1 Toxo d lum p e c p tated comb ed w th d ph h r a t o d 2 T xo d alum pre-c p t ted	0 5 l d 1 c b taneously	1 yr	Booster jec t an ually nd mmediate-ly on e p e	Moder te local	Oft n c mb ned with d phther sometimes w th pertus mm iz t on

TABLE 10B —ACCLPTTD METHODS OF ACTIVE IMMUNIZATION PROCEDURES TO BE USED WHEN INDICATED*

D	I d to s	M t ial U d	M th d d Do g	D r t n f Imm ty	R p t Imm iz t	Ad R t o	C mm ts
Cholera	*When t tel ng to e r ub e there is dang of p dem c r endem c holer (see Tabl 11)*	Vaccine 8 000 m llion k ll d cholera vib os per cc	*0 5 and 1 cc s b uta sly 7–10 d p t*	6 12 mo	*1 c. e ery 6 mo*	No severe reactions	
Plague	*When t l g to pl g e a at (t e T bl 11)*	Vacc 2 000 mill on pl gue bac lli pe cc	*0 5 nd 1 cc s b a an u ly 7 da. p t*	4 6 mo	*1 c ery 4 6 m*	Common but not serio s	
Rocky Mounta n spotted fever	*I are s ub a d s e s e dem c (s T ble 11)*	Egg yolk sac v ine	*2 dos s of 2 cc a h sub ta e o sly 1 uk ap t*	1 yr	*B oster i jec t o of 1 cc annually 6 u k b fo onset of t k season*	None se o s	
Typho d a d p ratypho d fevers	*When t l ng t eas u ber d se s t are nd m c o t al areas u th nad quate san t t on*	B cteri l s s pens on 1 000 m llion m cro o gan sms per cc.	*0 5 cc 1 cc nd 1 cc subcutaneo ly t ue kly s ter lt sm ller d ses n ch ld en*	Abo t 2 y	*Boo ter injec t n every seco d spri g f xposure conti u s*	Loc l and spl n ic reacti ns common b t not serious	
Typhus fever (pidemic type)	*Whe t l g t typh s ar as (Tabl 11)*	Egg yolk s c vacc ne	*2 doses of 1 cc each s b ut neo r ly 7–10 da. p t*	6–8 mo	*1 cc every 4–6 mo if xposu e co t nues*	No se e e react o s	
Y llow fever	*Wh n t vel g t rt n ar s (T ble 11)*	Concentrated gg y lk s c e	*0 5 cc of f hly pr par d 1 10 d l t s bc t n sly*	Probably 2–4 yr	*0 5 cc after 2 y f exp c t es*	M t NOT be given w th cowpox iru or to persons with rus d sease	

*The proced res recomm ded for most of these d seases are those mploy d by th Med cal Departm nt of the United States N vy

TABLE 11—CHIEF GEOGRAPHIC DISTRIBUTION OF IMPORTANT DISEASES REQUIRING IMMUNIZATION

DISEASE	LOCALITIES
Cholera	India and many parts of Asia
Plague	Asia Africa certain parts of South America and the Azores central Siberia sporadic cases in all major seaports and in the western part of the United States
Rocky Mountain spotted fever	Cases have been reported in all but one state of the U.S.A.
Smallpox	Mainly in Asia Turkey and parts of Europe but sporadically throughout the world
Typhus fever	North Africa, Asia and higher altitudes of Central and South America in parts of Europe where poor social conditions exist
Yellow fever	Tropical South America Africa Hawaii also in parts of Canada

DEFINITIONS (cont)

Toxoid Toxin modified usually by chemical action such as the addition of formalin. If properly prepared such modified toxins re tain their ability to elicit the specific antitoxic response in animals and in man but lose their toxicity They therefore present a most useful agent for active immunization.

Fluid toxoid Toxoid as is For human immunization it is care fully standardized for content of toxoid and tested for unimpaired ability to elicit immunity response (antigenicity)

Alum precipitated toxoid Fluid toxoid to which alum has been added. The toxoid is adsorbed on the alum and is slowly released when injected Thus antigen enters the circulation in smaller amounts but over a more extended period This is conducive to an improved antibody response

CONCENTRATION AND MODIFICATION OF THERAPEUTIC SE RUMS—In the description of the various serums it will be noted that they are often referred to as concentrated or refined and as

modified or despeciated It is important to understand the meaning of these terms

All therapeutic serum sold in this country is concentrated and refined by some one variant of the method of precipitation by sulfate ions By this method a considerable amount of potentially reaction producing but immunologically inert protein is eliminated and the volume necessary for injection of effective amounts of antibody is greatly reduced

However such serums retain their ability to elicit antibody against some of the protein of the serum—*e g* horse serum protein—and to cause reactions in persons hypersensitive to the respective proteins Such undesirable activity of antitoxins made in the horse can be greatly reduced although not completely eliminated by digestion of the serum with pepsin under suitable conditions As a consequence the incidence and seriousness of serum sickness is greatly diminished Use of such serum does not protect with certainty against the rare accidents from injection of antitoxin in atopically hypersensitive persons Serum treated by the digestion method is commonly designated modified and the process is called despeciation (from the elimination of the species specificity of the serum)

FEDERAL SUPERVISION OF BIOLOGIC PRODUCTS

The government exercises a certain amount of supervision over all *therapeutic* agents in interstate commerce through the Food and Drug Administration and the Federal Trade Commission This affords some protection against unfounded or fraudulent claims regarding therapeutic effect and potency and also safety of commercially available therapeutic products

Biologic products—the therapeutic serums vaccines etc—are much more effectively controlled and regulated by the National Institute of Health under the Regulations for the sale of viruses serums toxins and analogous products (1941)[1] Each individual

[1] Obtainable from U S Government Printing Office Washington D C

item is subject to detailed regulations for production and to standards of safety and potency A license must be obtained after evidence has been presented that proper facilities for production and testing are employed In addition the product is checked at the National Institute of Health from samples submitted by the manufacturer or purchased in the market. Thus the uniformity and safety of *biologic therapeutic agents are effectively safeguarded*

For *diagnostic* agents for human use no such strict supervision is provided Regulations in this respect are under consideration All therapeutic products described in the following chapters are manufactured by firms approved by the National Institute of Health

CARE OF VACCINE AND SERUM USED IN IMMUNOLOGIC PRACTICE

Always look at the expiration date

Don t use a material after date of expiration

Keep in the refrigerator at about 40 F but not in the freezing compartment Freezing usually does not impair the potency of the material but repeated alternate freezing and thawing may The one exception is vaccinia virus which should always be kept at freezing temperature

Warm to room temperature before using Heating to 98 F may lessen or destroy the protective value

IMMUNIZATION IN PEDIATRIC PRACTICE

Since many of the infectious diseases characteristically occur during infancy and childhood and since most prophylactic procedures are employed in these age periods some special pediatric problems are described in the following paragraphs

NATURAL IMMUNITY TO CONTAGIOUS DISEASES OF CHILDHOOD —The newborn up to 2 months of age is usually *immune* to such diseases as *measles diphtheria scarlet fever mumps* and *poliomyelitis* because of antibody transferred from the mother He is however *susceptible* to certain diseases from birth *whooping cough*

smallpox erysipelas, chickenpox and *meningococcic* and other forms of *meningitis*

Schedule for Routine Immunizations and Tests

1 *At 3 months* smallpox vaccination
2 *At 6 months* start whooping cough injections
3 *At 9 months* start combined diphtheria tetanus injections
4 *At 14 months* Schick test, if positive repeat injection of diphtheria toxoid
5 *At 3 years* booster whooping cough injection tuberculin test
6 *At 5–6 years* booster diphtheria and tetanus injections re peat smallpox vaccination tuberculin patch test

Under the following circumstances routine immunizations are indicated

7 *Childhood accidents* booster tetanus toxoid injection when in dicated rabies inoculations when indicated
8 *On going to country or camp* typhoid paratyphoid vaccine in jections
9 *In areas where disease is endemic* vaccination against Rocky Mountain spotted fever generally accepted as of value
10 *At the first warning of impending influenza epidemic* protec tion by immunization with influenza vaccine

USE OF HUMAN SERUMS IN INFECTIOUS DISEASES—*Normal serum* is obtained from normal human volunteers not suffering from nor recently recovered from a disease Since previous contact with and, therefore immunity to the common infectious diseases in most adults can be assumed such serum usually has immune bodies and may be of therapeutic help to a patient with a commonly en countered infectious disease if the specific convalescent serum is not obtainable

Immune globulin is a concentrate of serum proteins containing the antibody bearing fraction It is usually obtained from placentas although it may be fractionated from blood plasma

Convalescent serum is a specific serum obtained from a volunteer who has recently (1–3 months) recovered from the particular disease

Hyperimmune serum is a specific serum obtained from a volunteer who has recently recovered from a particular disease and whose blood antibody content to this disease has been further raised by active immunization with products of the disease agent

The value of these biologic materials for prophylaxis and treatment of various diseases may be summarized as follows

1 Generally accepted as of value in *prophylaxis* normal serum and immune globulin in *measles* convalescent serum in *scarlet fever*

2 Said to be of value in *prophylaxis* hyperimmune serum in *whooping cough* convalescent serum in *poliomyelitis mumps varicella anthrax*

3 Generally accepted as of value in early *treatment* convalescent serum in *scarlet fever*

4 Generally said to be of some value in *treatment* hyperimmune serum in *whooping cough* immune globulin in the pre-eruptive stage of *measles* convalescent serum in *mumps varicella preparalytic poliomyelitis undulant fever* and *Rocky Mountain spotted fever* (In the *prophylaxis* and *treatment* of *preparalytic poliomyelitis* normal pooled adult serum is considered about as effective as convalescent serum In *prophylaxis* and *treatment* of *scarlet fever* pooled serum is about one fourth as effective as convalescent serum)

5 Generally considered of *no* value although tried in *staphylococcic* and *influenzal septicemia* and in *meningitis*

Availability of these serums is limited The physician wishing to obtain them should inquire of the nearest serum center Recognized serum centers are

SAMUEL DEUTSCH CONVALESCENT SERUM CENTER Michael Reese Research Foundation, 2912 Ellis Avenue Chicago 16
Measles Convalescent Serum 5 cc 7 5 cc. and 20 cc vials
Scarlet Fever Convalescent Serum 5 cc 7 5 cc. and 20 cc. vials
Poliomyelitis Convalescent Serum (available to Illinois residents only)

MILWAUKEE CONVALESCENT SERUM CENTER, Columbia Hospital 3321 N Maryland Avenue Milwaukee 11
Measles Immune Serum 5 cc. and 7 5 cc vials
Scarlet Fever Immune Serum 10 cc. and 20 cc vials
Pertussis Immune Serum

PHILADELPHIA SERUM EXCHANGE Childrens Hospital 1740 Bainbridge Street Philadelphia 46
Measles Immune Serum sufficient frozen and dried serum to furnish 10 cc and 20 cc of restored serum
Scarlet Fever Immune Serum 10 cc 15 cc. and 20 cc vials
Pertussis Immune Serum

HUMAN SERUM LABORATORY University of Minnesota, Minneapolis

DES MOINES SERUM CENTER, Iowa State Department of Health Des Moines.

HYLAND LABORATORIES 4534 Sunset Boulevard Los Angeles 27

Further information regarding procurement and use of human serums may be obtained from the American Human Serum Association 348 West 22d Street New York City

Hyperimmune pertussis serum is also manufactured by commercial houses in 2 5 cc (one dose) vials equivalent to 50 cc of whole blood from hyperimmunized human donors Immune globulin may be obtained from most of the large commercial houses in addition to the human serum centers These firms are listed under specific disease entities

General considerations in the use of these serums are

1 Like all serums they should be used early and in full doses

2 Although untoward reactions are rare from material of human origin they have been reported

3 Administer intravenously for rapid and maximum effect.

4 Warm serum to body temperature before use

5 Inject slowly and continuously

6 Use a syringe (not continuous intravenous drip) and *do not* inject together with glucose or saline solutions

7 Absolute sterility is essential

8 Do not insert the needle into the bottle more than once Remove full dose of serum at one time

9 Do not withdraw blood into the syringeful of serum Once it has been determined that the needle is in the vein inject steadily and slowly

Use of human blood serum is not entirely without complications One possibility is the occurrence of homologous serum hepatitis The over all incidence of hepatitis following the administration of some lots of plasma is well under 2 per cent however a high incidence may be expected in a group of persons who have received plasma serum or whole blood containing the infective virus Since the incubation period is 30–180 days blood donors should not be accepted if they have received plasma whole blood or convalescent serum during the past eight months or if they have had jaundice within the past year

PREVENTION OF CONTAGIOUS DISEASES ON A PEDIATRIC WARD OR IN OTHER INSTITUTIONS —1 Active immunization is strongly recommended as a long range procedure in institutions admitting children for prolonged stays This is accomplished by the following types of injections

a) Altered live virus *smallpox* (after exposure)

b) Killed bacterial suspensions *whooping cough typhoid*

c) Toxins modified (toxoids) *diphtheria, scarlet fever whooping cough tetanus*

2 Passive immunization is performed for immediate temporary protection—when faced with an epidemic This is accomplished by the following types of injections

a) Antitoxin *diphtheria scarlet fever*

b) Convalescent serum *measles mumps* and when antitoxin is not available or is contraindicated during a threatened outbreak of *scarlet fever*

c) Human immune globulin *measles*

Routine injection with human serum of every patient admitted to a pediatric ward is reported by some to be of value in keeping the service free of infection particularly of measles thus avoiding the closing of wards for quarantine Pooled serum (blood bank) or individual serum (parents) in 20–30 cc amounts is used *intramuscularly*

Botulism

INCUBATION PERIOD

Several hours to one or more days

PRODROMAL SYMPTOMS

Weakness dizziness disturbances of eyes and of pharyngeal and respiratory musculature

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

No immunologic method available

TREATMENT

Antitoxin produced and combined from types A and B Clostridium botulinum is considered to be of value

Indications —Botulism is a form of poisoning not an infection Unfortunately early diagnosis and specific therapy are not feasible in isolated cases In mass poisoning however early diagnosis is made possible by history and investigation of the first cases and specific treatment with antitoxic serum is of value because it can be given early An individual exposed to botulinus toxin must be treated even before the onset of symptoms because of the rapid course and high mortality if such prophylaxis has not been carried out.

Material

Jensen Salsbery Laboratories Inc. bivalent antitoxin in vials of 2 500 units each of types A and B

Lederle Laboratories Inc. *bivalent antitoxin in vials of* 10 000 units each of types A and B

Method—An injection of 10 000 units is given *intravenously* as soon as the diagnosis is established The dose should be repeated every four hours until the toxic symptoms subside

Contraindications—The same as those for any horse serum

IMMUNITY

None

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Home canning is the usual source of this poisoning Prevention depends on proper preservation of food.

Brucellosis (Undulant Fever)

INCUBATION PERIOD

Usually from 6 to 30 days but often longer

PRODROMAL SYMPTOMS

Irregular The disease may be acute or chronic

PROPHYLAXIS

No generally accepted immunologic method available

DIAGNOSIS

There are four methods which may be used to confirm the clinical diagnosis of brucellosis *culture agglutination reactions, opsonic blood tests* and *skin testing* When the diagnosis is suspected all four technics should be employed. The skin test is the only one which is discussed here as an office procedure

The diagnosis follows only after consideration of the results of culture agglutination tests and skin test in relation to the clinical symptoms Recovery of the micro-organism is definite evidence of infection The other tests when positive may indicate previous ex posure rather than active present infection A negative skin test is considered strong evidence for ruling out brucellosis Ascertaining the *opsonic index* requires skilled personnel The agglutination test may soon become a simple procedure since the Pitman Moore Com pany now issues a 5 cc vial of Brucella antigen for rapid office agglutination tests

SKIN TEST —The skin test is at present the only practicable office procedure the others requiring that material be sent to a properly equipped laboratory Whenever a skin test with *brucellergen* is performed it is wise to take a blood sample for an agglutination test at the same time For if the skin test is negative an agglutination test may be required later and then a false positive reaction may result from the previous exposure to the skin test antigen In general it is advisable to take material for blood cultures and agglutination tests before or at the same time the skin test is performed

Indication —Suspicion of Brucella infection

Materials —Although any of the vaccines listed under treatment can be used for the diagnostic skin test the generally accepted material for this purpose is Brucellergen which is obtained in 1 cc vials from

Central Brucella Station Michigan State College East Lansing Michigan.

Methods —Brucellergen Test Inject 0 1 cc of the brucellergen *intracutaneously* using the lateral surface of the forearm Read in 48 hours Some advise a reading as late as seven days after the performance of the test The degrees of reaction are described in the instruction sheet which accompanies the material in general a positive skin test consists of erythema *and* edema or induration

Vaccine Test The vaccine is diluted 1 10 with sterile saline solution In the case of a child it may be better to dilute this dilution further 1 5 Inject 0 1 cc of this diluted vaccine *intradermally* Read immediately for urticarial response read again at 12 hours and at 48 hours for tuberculin type reactions

TREATMENT

Indications —Treatment with the sulfonamides penicillin and specific antiserums has been disappointing Streptomycin appears to offer more promise Hyposensitization with specific brucellin or vaccine is worthy of trial In judging the effects of the vaccine it should be remembered that in a not inconsiderable number of cases there is spontaneous termination of the disease

Materials—The material most generally regarded as giving good results in specific treatment is Brucellin which is distributed in 2 cc vials by

Central Brucella Station Michigan State College East Lansing Michigan.

The following vaccine preparations prepared from killed micro-organisms, are also accepted as of value

Jensen Salsbery Laboratories Inc. 1 cc vials 3 billion each of Br abortus (bovine) and Br suis (porcine) per cc

Lederle Laboratories Inc 5 cc vials containing 1 billion each of killed Br abortus and Br suis per cc

National Drug Co 30 cc 15 cc and 5 cc vials containing 2 500 million each of killed Br abortus and Br suis per cc 5 cc., 15 cc and 30 cc vials containing 2 500 million killed Br melitensis (caprine) per cc.

Parke Davis & Co 5 cc vials containing 1 billion each of killed Br abortus and Br suis per cc

Pitman Moore Co 5 cc and 20 cc vials containing 1 000 million each of Br abortus and Br suis per cc

Sharp & Dohme Inc Brucella Abortus Bacterin in 5 cc vials containing 2 000 million bacilli per cc

Wyeth Inc 12 cc vials containing 1 000 million each of Br abortus and Br suis per cc

Methods—Complete instructions for the use of brucellin come with the vial The efficacy of the agent depends on the existence and continuation of a state of sensitization in the patient while under treatment First administer an *intradermal* injection of *0 1 cc* brucellin to determine the patient s sensitivity *If there is no reaction in* 24 hours give 0 5 cc intradermally If there is a local and general reaction repeat after an interval of three days Repeat every three days until no reaction occurs from the injection Then increase the dose to 1 cc *intracutaneously* and *intramuscularly* continue until no hypersensitive reaction can be obtained

The vaccine standardized to 2 billion micro organisms per cc is injected intracutaneously or subcutaneously Dosage is 0 2 cc daily

for the first three days, 0 3–0 5 cc for the next three days, and then 1 cc daily for 10–15 doses

Contraindications—Local and general reactions occur Vaccine treatment or injection with brucellin is contraindicated in a patient with heart disease renal disease arteriosclerosis diabetes pernicious anemia aplastic anemia or epilepsy in meningeal or cerebral localization of Brucella and in the acute fulminating form of the disease

IMMUNITY

Clinical infection usually results in protection against reinfection.

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Undulant fever is transmitted by ingestion of infected milk or by handling infected cows goats or hogs meat Elimination of the disease depends on the slaughter and destruction of infected animals, *the immunization of calves increased caution (rubber gloves) in* handling meats and insistence on pasteurization of all milk.

Chickenpox (Varicella)

INCUBATION PERIOD

Fourteen to 18 days

PRODROMAL SYMPTOMS

Slight fever and malaise before the appearance of the eruption

PROPHYLAXIS

ACTIVE IMMUNIZATION—None available

PASSIVE IMMUNIZATION—*Human convalescent* chickenpox serum is obtainable from the serum centers listed on page 103 It is generally of some value *Inject 20 cc intramuscularly as early after exposure as possible* It is especially indicated in infants under 1 year

DIAGNOSIS

No immunologic methods either for diagnosis or for ascertaining presence or absence of susceptibility are available at present.

TREATMENT

In a severe case *intramuscular* injection of 30–40 cc. of human convalescent serum may be of some value

IMMUNITY

One attack of the disease confers immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Isolation until the rash has subsided is essential some believe isolation should be continued until the crusts have fallen off Spread may occur chiefly by direct contact but also possibly through a third person. As far as is known carriers do not play a role in transmission

Cholera

INCUBATION PERIOD

Several hours to five days

PRODROMAL SYMPTOMS

Diarrhea and malaise

PROPHYLAXIS

ACTIVE IMMUNIZATION —*Indications* —Persons living or travel ing in areas in which cholera is prevalent and laboratory personnel working with the micro-organism should be immunized.

Material —Cholera vaccine is prepared by the following firms

Connaught Laboratories (University of Toronto Toronto 5 Canada) 2 5 cc. vial containing sufficient vaccine for in oculation of one person 10 cc. vial for inoculation of from four to six persons

Lederle Laboratories Inc. 20 cc. vials containing 8 000 million killed micro organisms per cc

Eli Lilly and Co three 1 cc vials one containing 500 mil lion and two containing 1 000 million killed micro-organisms also packages of 10 vials containing 1 000 million killed micro-organisms per cc each vial sufficient for one immunization

Wyeth Inc three 1 cc vials Immunizing Dose No 1 containing 4 000 million killed micro organisms per cc Immunizing Doses No 2 and No 3 containing 8 000 million killed micro organisms per cc also bulk 20 cc vials containing 8 000 million micro organisms per cc

Method—The first dose of 0 5 cc of the vaccine is given *subcutaneously* followed in seven days by a second dose of 1 cc When a set of three vials is sold for a series of injections for a single immunization the vial for the first dose contains 1 cc by volume but only half the number of organisms in the other two vials A booster dose of 1 cc is given *intracutaneously* every six months for the duration of possible exposure to cholera

There are no *contraindications* to the use of this vaccine

PASSIVE IMMUNIZATION —No immunologic method is available

DIAGNOSIS

No immunologic method available

TREATMENT

No immunologic method is available The use of sulfadiazine or penicillin and blood plasma is generally accepted as of great value in treatment

IMMUNITY

One attack probably does not confer immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Prevention of the disease depends on active immunization the safeguarding of the sewage disposal system and the early strict isolation of new cases

Common Cold

INCUBATION PERIOD

Several hours to three days

PRODROMAL SYMPTOMS

Malaise headache sneezing fever

PROPHYLAXIS

Although numerous vaccines both for oral and subcutaneous use have been prepared there is no clinical evidence for their efficacy

DIAGNOSIS

No immunologic method available

TREATMENT

No effective immunologic method available

IMMUNITY

Previous attacks do not confer immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Prevention depends on strict isolation of the individual immediately on appearance of the first symptom of the disease

Diphtheria

INCUBATION PERIOD

Two to eight days

PRODROMAL SYMPTOMS

Symptoms of upper respiratory tract infection

PROPHYLAXIS

ACTIVE IMMUNIZATION —Diphtheria toxoid alum precipitated is generally considered most desirable for active prophylaxis

The problem of eliminating or diminishing undesirable by reactions to diphtheria and/or tetanus toxoids in adults became of interest to the Armed Forces as a consequence of their extensive immunization program Systematic investigation led to the development of a method for the purification of diphtheria and tetanus toxoids This method based on precipitation by alcohol under controlled conditions yielded toxoids of high antigenicity which on clinical trial were remarkably well tolerated The corresponding alum precipitated toxoids contain considerably less alum than do those made with nonpurified toxoids The volume of the single immunizing dose is in every case 0 5 cc The schedule of immunization remains unchanged The new toxoids which became commercially available during the time this book was in press are replacing the respective Lederle products and are marketed under the trade mark Purogenated

Diphtheria Toxoid Fluid Purogenated 1 5 cc. and 7 5 cc vials for one and five immunizations

Diphtheria Toxoid Fluid Purogenated 1 5 cc. and 7 5 cc vials for and 5 cc vials for one and five immunizations

Diphtheria Tetanus Toxoid Refined Alum Precipitated Purogenated 1 cc. and 5 cc. vials for one and five immunizations

Indications

a) Routine prophylaxis in every infant at 9–12 months of age Toxoid is preferred for this purpose A Schick test is done six months later and an additional injection is given if it is positive

b) A booster injection on entering school

c) Children of any age who have a positive Schick test if about to enter an institution or hospital

d) Adults with a positive Schick test who are employed in a contagious disease hospital

Combined Immunization—Recently there has been a tendency to immunize the child to more than one disease at a time by giving injections of the different antigens concurrently or by administering combinations of antigens simultaneously Advantages of these com binations are (1) a reduction in the number of injections needed to give the child adequate protection (2) earlier complete protection and (3) the lower cost and increased convenience in administration It is reported that the antigenic response at least so far as can be ascertained in the laboratory is as satisfactory as with the older technics One disadvantage is the possible tendency to start immuni zation against pertussis a little later and against diphtheria a little earlier than the optimal time The tetanus diphtheria combination is generally accepted as having no contraindications The tetanus diphtheria pertussis combination is generally accepted as being of some value but in each case the Schick test should be done to ascer tain the status of diphtheria immunity

Materials—Diphtheria Toxoid Alum Precipitated[2] is generally ac cepted as of greatest value in active immunization against diphtheria. It is prepared by the following firms

Cutter Laboratories 1 cc and 10 cc. vials
Lederle Laboratories Inc. 0 5 cc 1 cc 5 cc and 10 cc vials
Eli Lilly and Co 0 5 cc and 5 cc vials
National Drug Co 0 5 cc 1 cc. and 5 cc. vials
Parke Davis & Co 0 5 cc. 1 cc 5 cc. and 10 cc vials
Pitman Moore Co 1 cc and 10 cc vials

Sharp & Dohme Inc 2 cc., 5 cc. and 10 cc. vials

E. R. Squibb & Sons 1 cc. and 10 cc. vials also for small dose preference 0 5 cc. and 5 cc. vials equal in immunizing potency to the 1 cc. and 10 cc. vials respectively

U S Standard Products Co 1 cc. and 10 cc. vials

Wyeth, Inc. 0 5 cc., 1 cc., 5 cc. and 10 cc. vials

Diphtheria Toxoid, aluminum hydroxide adsorbed (alhydrox) is prepared by

Cutter Laboratories for one and five immunizations

Diphtheria Toxoid (Fluid)[2] is prepared by

Cutter Laboratories 1 cc. and 30 cc. vials

Lederle Laboratories Inc. 1 cc. and 30 cc vials accompanied by diluted toxoid for reaction test.

Eli Lilly and Co 1 cc. and 30 cc. vials

National Drug Co 3 cc. vials

Parke Davis & Co 0 5 cc. and 1 cc. bulbs 30 cc. vials

Sharp & Dohme Inc. 3 cc. and 30 cc. vials

E R. Squibb & Sons 1 cc and 30 cc. vials accompanied by 1 cc. vial for reaction test, sufficient for 10 tests

U S Standard Products Co 1 cc., 6 cc., 20 cc. and 30 cc. vials

Wyeth, Inc. 1 cc. and 30 cc. vials accompanied by diluted toxoid for reaction test

Diphtheria Toxoid Tetanus Toxoid, Alum Precipitated Combined[2] is obtainable from the following concerns in packages of two 1 cc vials and one 10 cc. vial.

Cutter Laboratories	Parke Davis & Co
Lederle Laboratories Inc	E R. Squibb & Sons
Eli Lilly and Co	Wyeth, Inc.

This product is also available for one immunization in packages of two 1 cc vials and for five immunizations in packages of two 5 cc. vials from

National Drug Co

Diphtheria Toxoid, Alum Precipitated Pertussis Vaccine Combined, is obtainable from

Cutter Laboratories aluminum hydroxide adsorbed toxoid, in packages for one and five immunizations

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[2] See footnote pag 113

Indications

a) Routine prophylaxis in every infant at 9–12 months of age Toxoid is preferred for this purpose A Schick test is done six months later and an additional injection is given if it is positive

b) A booster injection on entering school

c) Children of any age who have a positive Schick test if about to enter an institution or ho pital

d) Adults with a positive Schick test who are employed in a contagious disease hospital

Combined Immunization—Recently there has been a tendency to immunize the child to more than one disease at a time by giving injections of the different antigens concurrently or by administering combinations of antigens simultaneously Advantages of these com binations are (1) a reduction in the number of injections needed to give the child adequate protection (2) earlier complete protection and (3) the lower cost and increased convenience in administration. It is reported that the antigenic response at least so far as can be ascertained in the laboratory is as satisfactory as with the older technics One disadvantage is the possible tendency to start immuni zation against pertussis a little later and against diphtheria a little earlier than the optimal time The tetanus diphtheria combination is generally accepted as having no contraindications The tetanus diphtheria pertussis combination is generally accepted as being of some value but in each case the Schick test should be done to ascer tain the status of diphtheria immunity

Materials—Diphtheria Toxoid, Alum Precipitated," is generally ac cepted as of greatest value in active immunization against diphtheria. It is prepared by the following firms

Cutter Laboratories 1 cc. and 10 cc. vials
Lederle Laboratories Inc 0 5 cc 1 cc 5 cc and 10 cc. vials
Eli Lilly and Co 0 5 cc. and 5 cc. vials
National Drug Co 0 5 cc. 1 cc. and 5 cc vials
Parke Davis & Co 0 5 cc 1 cc 5 cc. and 10 cc vials
Pitman Moore Co 1 cc. and 10 cc. vials

Diphtheria Tetanus Pertussis Combined Alum Precipitated Combined immunization with all three antigens is reported to be of some value Adverse reactions are reported to be more frequent than those in diphtheria immunization alone but less frequent than those from pertussis vaccine injections The combined form is given *subcutaneously* in three doses of 1 cc each at four week intervals The aluminum hydroxide adsorbed material is given in doses of 0 5 cc 0 5 cc and 1 cc at monthly intervals

No matter what the material or the method immunity to diphtheria is tested by the Schick test six months after completion of the inoculations If the test is positive an additional injection is given When the child begins school an additional or booster injection of 1 cc. alum precipitated toxoid is indicated without a preliminary Schick test

Contraindications —Local and general reactions to alum precipitated toxoid are infrequent and mild in children under 10 In a large series of cases less than 0 3 per cent required a home visit because of fever or local pain Older children and adults however suffer a higher incidence and a greater severity of reactions after toxoid injection In these persons diluted toxoid should first be injected intradermally to determine sensitivity The reaction to mixed immunization is more severe than with single injections Nodulation is common and abscesses may occur Nodulation is said to be rare with the alum adsorbed toxoid

PASSIVE IMMUNIZATION —*Indications*

a) In infants under one year exposed to a patient with diphtheria

b) In children over one year who have a positive Schick test and have been exposed (particularly important in an institutionalized group)

c) If exposure is prolonged beyond three weeks an additional immunizing injection is needed

It is essential in the event of a threatened epidemic to identify and isolate the diphtheria carriers

Material—Diphtheria Antitoxin is used Available preparations packaging etc are listed under diphtheria treatment

Method—After testing for serum sensitivity inject 1 000 units *intramuscularly* This confers immunity almost immediately Immunity lasts about three weeks

Contraindications—All precautions relating to serum sickness and anaphylaxis apply Avoidance of such reactions is obtained by the use of modified horse serums or serums from other animals

DIAGNOSIS

No immunologic method for definite diagnosis is available However the Schick test is generally used to ascertain the presence or absence of adequate amounts of antitoxin and hence the individual s immunity or susceptibility to the disease

SCHICK TEST —*Indications*

a) To determine immunity after active immunization and thus to assay its success This test is recommended six months after the immunization although it is often omitted in infants

b) To determine the need for active immunization of an adult or an older child No individual over 10 years of age should be immunized without a preliminary (positive) Schick test In a child under 1 active immunization is started without a preliminary Schick test For practical reasons the booster dose is also generally given the preschool child without benefit of a preliminary Schick test The test should be performed on entering high school

c) To determine immunity before administering antitoxin for passive immunization

d) The test is generally of *no* practical value in the diagnosis of the disease

e) The test is apparently of little or *no* value for determining immunity in diphtheria of the skin

Material—Diphtheria Toxin for the Schick Test diluted and ready for use is manufactured by the following pharmaceutical houses

Cutter Laboratories vials for 10 tests

Lederle Laboratories Inc. vials for 10 and 50 tests also heated diphtheria toxin in vials containing material for 10 control tests.

Eli Lilly and Co vials for 10 and 100 tests

National Drug Co vials for 10 50 and 100 tests also heated toxin in vials for 10 and 50 control tests

Parke Davis & Co vials for 10 50 and 100 tests also heated toxin for control tests

Pitman Moore Co vials for 10 tests

Sharp & Dohme Inc vials for 10 50 and 100 tests also heated toxin in vials for 50 control tests

E. R. Squibb & Sons vials for 10 and 100 tests also heated material for 100 control tests

Wyeth Inc. vials for 10 25 and 50 tests also heated toxin for 10 25 and 50 control tests

Concentrated toxin is supplied with diluent by

Cutter Laboratories vial for 50 tests after dilution

Method—Inject 0 1 cc of the toxin *intracutaneously* into the skin of the volar surface of the forearm The toxin should be fresh if diluted with saline If diluted with peptone solution (Lederle) the diluted toxin is said to remain potent for a week The control test is done on the corresponding site of the opposite arm using a heated toxin for the purpose

Negative Reaction—The test is read as negative if there is no response at either site or if both sites have an equal (pseudo) reaction of redness and edema Pseudoreactions are due to sensitization to the protein in the toxin preparation Since they are not common in the first five years of life in that period the control test is not performed The pseudoreaction usually reaches its height earlier (24 hours) and disappears earlier (48 hours) than does the true reaction This pseudoreaction is generally less circumscribed and does not leave a brown pigmentation

Positive Reaction—The positive reaction appears in 24 hours and continues to develop until 48–72 hours It should be read at 72 hours It appears as an area of redness and edema 1–2 cm in diam

eter The reaction remains 6–12 days and leaves a lightly pigmented spot The control site shows no reaction unless the positive reactor is also sensitive to the bacterial protein In this case the reaction will be smaller than the test site reaction will have less edema and will exhibit the other characteristics of pseudoreactions

A positive reaction means there is insufficient antitoxin to neutralize the injection of 1/40 M L D of diphtheria toxin A negative reaction means that there is enough antitoxin to effect the neutralization A person possessing enough antitoxin to confer a negative Schick test will probably be able to ward off the average infection with Corynebacterium diphtheriae

Contraindications—Dangers are few Occasionally an individual will develop a vesicular type of reaction and rarely a local necrosis Such reaction is somewhat more frequent if the test is done while the child is suffering from an acute infectious disease or in those who have a very low serum antitoxin titer

TREATMENT

Indications—Whereas nursing care and general medical treatment are of utmost importance in the treatment of diphtheria particularly in croup and in the prevention and treatment of cardiac failure the *ultimate prognosis depends on the early administration of adequate doses of antitoxin* Use antitoxin in every case and use it early for the case which seems mild on the first day may become serious overnight Antitoxin will not undo the damage already wrought by the toxin

Antitoxin will not materially affect the tonsillar membrane already present at the time of administration

Antitoxin is generally of no value in the treatment of post diphtheritic neuritis It appears to be of little value in the treatment of skin lesions

Material—Refined and Concentrated Diphtheria Antitoxin is packaged in syringes ready for use or in vials by the following pharmaceutical houses

Cutter Laboratories vials of 1 5 10 20 and 40 thousand units.

Lederle Laboratories Inc. vials of 1 10 and 20 thousand units

Eli Lilly and Co vials of 1 5 10 20 and 40 thousand units

National Drug Co syringes of 1 3 5 10 and 40 thousand units vials of 1 5 10 and 20 thousand units

Parke Davis & Co vials of 1 5 10 and 20 thousand units

Pitman Moore Co syringes of 1 and 10 thousand units vials of 20 000 units

E. R. Squibb & Sons syringes of 1 5 and 60 thousand units vials of 1 5 10 and 20 thousand units

Method—Before the use of any serum a careful history in regard to atopy should be taken and ophthalmic or intradermal tests should be performed to rule out sensitivity to the serum If the patient is or may be sensitive to horse serum modified antitoxin or antitoxin produced in some other species of animal should be used. If these are not available *the method of desensitization* described on page 87 is generally considered to be of some value

The injections may be given *intramuscularly* in the buttocks but are most often given *intravenously* particularly in severe cases or in those receiving treatment late In the latter cases and in laryngeal cases give *40 000–60,000 units intravenously* If the dose is gaged accurately usually only one injection is necessary If there is a progression of the disease in 24 hours the dose must be repeated In mild localized diphtheria 100 units per lb of body weight is given

Early treatment is essential If the clinical appearance of the throat is suspicious give a small dose of antitoxin immediately even before the result of the culture is known In malignant diphtheria scarlatinal streptococcus antitoxin is also generally considered of value The dosage corresponds to that described for treatment of scarlet fever

Contraindications—The dangers are those of sensitivity to horse serum Measures to prevent and to treat constitutional reactions and serum sickness have been described

IMMUNITY

Newborn infants enjoy immunity passively acquired from the mother provided the mother has a sufficiently high antitoxin titer This immunity disappears rapidly and at *6–9 months* most babies have a positive Schick test Acquisition of immunity by subclinical exposure is widespread as shown by the increasing incidence of negative Schick tests with increasing age However 15 per cent of adults show a positive Schick test Immunity acquired after an attack of the illness may not be permanent if it has been treated massively with antitoxin Second attacks occur in about 1 per cent of cases Immunity by injections is obtained within one to six months depending on the method and lasts for four to six years

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Active immunization of all children and all other susceptible persons is generally considered of utmost importance

All cases are produced by respiratory contact with material from the respiratory tract or other infected tissues of an infected patient or carrier Patients should be isolated until the throat culture or culture from other sites of infection is negative or in accordance with local regulations Susceptible contacts are isolated for a week Carriers should be restricted in their movements and treated (penicillin) Milk borne epidemics occasionally occur

Dysentery

The overwhelming majority of diarrheal diseases is caused by bacteria of the genus Shigella (dysentery bacilli) of which some 20 different types are now known Some are caused by Salmonella (paratyphoid bacilli see p 178) others particularly in infants by micro-organisms related to the colon bacilli or proteus bacilli and by viruses Information on the incidence of the various dysentery bacilli has been forthcoming only during recent years since only lately have means been devised to make type-differentiation as rapid and expedient as the typing of pneumococci

INCUBATION PERIOD

Twelve hours to four days

PRODROMAL SYMPTOMS

Malaise headache nausea fever Frequently there is no period of prodromal symptoms

PROPHYLAXIS

There is no conclusive evidence of the value of prophylactic vaccination Prophylaxis by feeding of polyvalent bacteriophage has been recommended but its value is highly controversial and no commercial product is available

DIAGNOSIS

No method practicable for office use is available The bacteriologic examination of feces if reliably done will yield a high percentage of positive results which ought to be of considerable value for the appraisal of epidemiologic problems in family and community

Agglutinating antibodies in the serum are found only irregularly and appear too late to be of much immediate assistance in diagnosis The Widal test is occasionally of some help in the post festum exploration of outbreaks

TREATMENT

Treatment with sulfonamides particularly sulfadiazine is generally accepted as being of great value No therapeutic serum is available at the present time The only serum for which presumptive evidence of clinical usefulness has been established is the *antitoxin for the Shiga bacillus* However since this micro-organism is found only rarely in cases in this country and is the causative agent in only 10–15 per cent of cases in tropical countries this antitoxin can be expected to be of use only in a minority of cases and should be employed only when the causal role of Shiga s bacillus has been proved. Shiga antitoxin is usually of equine origin and its use necessitates the usual precautions against accidents from horse serum hypersensitivity

Therapy by ingestion of bacteriophage is as controversial as is prophylaxis No therapeutic bacteriophage preparations are available

IMMUNITY

One attack does *not* confer immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Dysentery is as a rule a food borne infection The micro organisms are brought to the food either by human carriers or by flies Thus food has to be protected from contamination by the often numerous human carriers and from flies Water borne outbreaks have been reported as exceptional occurrences

Encephalitis

There are no generally accepted immunologic office procedures for the prophylaxis diagnosis or treatment of encephalitis For epidemiologic reasons it is most important to report cases early and to submit blood or spinal fluid or post mortem brain tissue to the nearest properly equipped laboratory for the purpose of determining the type of infection—whether equine Japanese St Louis etc

Erysipelas

INCUBATION PERIOD

One to three days

PRODROMAL SYMPTOMS

Fever Especially in children vomiting chill convulsions

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

No immunologic method available

TREATMENT

Indications—Penicillin and the sulfonamides are the outstanding agents in the treatment of this disease However specific treatment with antitoxin is occasionally indicated as in patients who have had a previous adverse reaction to administration of these drugs and in severely ill patients particularly infants

Material—Erysipelas Streptococcus Antitoxin is supplied in 5 cc. 12 5 cc., and 20 cc. vials by

Sherman Laboratories, Inc.

Method—A full therapeutic dose usually 7 5 cc is given *intra muscularly* and repeated every 6–18 hours until signs of toxicity have subsided Concomitant treatment with a sulfonamide or peni cillin is continued whenever possible

Contraindications—The usual precautions against reactions to horse serum must be taken

IMMUNITY

An attack does not confer immunity Reinfections are common

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Erysipelas is not highly contagious as a rule However cases have been contracted through contact with infected wounds scarlet fever cases or their fomites laboratory material etc

Erysipeloid (Swine Erysipelas, Fish Handlers' Disease)

INCUBATION PERIOD

One to 3 days in exceptional cases up to 10 days

PRODROMAL SYMPTOMS

Malaise Often none

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

No reliable immunologic method is as yet available although skin tests with erysipeloidin and certain serologic reactions show some promise

TREATMENT

Indications—The apparent effectiveness of sulfonamides and penicillin appears to have reduced the necessity for serum treatment However every acute fulminating or persistent or recurrent case should also be treated with serum which is generally of value

Material—Antierysipeloid Serum is prepared by immunizing horses by injections of the bacillus of swine erysipelas (Erysipelothrix rhusiopathiae) It is supplied by

Pitman Moore Co 10 cc vials

Method—The serum is given *subcutaneously* or *intramuscularly* in doses of 10–20 cc a total of 100 cc every 12 hours is advised as long as symptoms persist In addition it is suggested that about 10 injections of 0 25–0 5 cc each be administered intracutaneously at the borders of the lesion

Contraindications—Precautions for horse serum administration are indicated Intramuscular injections are usually followed by local edema enlargement of regional lymph nodes and urticarial lesions near the site of infection Reactions are common because these serums prepared primarily for veterinarian use are not highly refined

IMMUNITY

There is no acquired immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Elimination of the disease in man depends on its elimination in swine Great care should be exercised in handling meat or fish

Filariasis

INCUBATION PERIOD

One to several months

PRODROMAL SYMPTOMS

Malaise depression frontal headache urticaria

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

No immunologic measures are as yet generally available However antigens prepared with Dirofilaria immitis (of the dog) have given promising results both in skin tests (reaction of urticarial hypersensitivity) and in serologic tests

TREATMENT

No immunologic method available

IMMUNITY

Adult filariae frequently are killed in the lymphatic vessels But it is not known whether an immunologic mechanism contributes to this

Urticaria and retrograde lymphangitis are frequently connected with attacks It is probable that an allergic response to the parasite and/or its products is a regular feature of the disease and perhaps even the principal pathogenic mechanism

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Infection is mosquito-borne several genera and species of mosquitoes are implicated

Gas Gangrene

This clinical syndrome can be caused by a variety of anaerobic micro-organisms (Clostridium) Infection usually takes place in a deep wound particularly where there has been destruction of muscle tissue It is severe and rapidly progressive and presents an emergency during which there is no time for exact bacteriologic studies The immune serums therefore are always multivalent and are designed to be effective for nearly all cases

INCUBATION PERIOD

Varies from several hours to two days

PROPHYLAXIS

ACTIVE IMMUNIZATION —None

PASSIVE IMMUNIZATION —*Indications* —Gas gangrene is a complication of deep destructive wounds in which there has been laceration of muscle The antitoxin is often given in combination with tetanus antitoxin to *any* patient who has suffered destruction of such tissue Its use is especially indicated in compound fractures after pro-

longed application of a tourniquet and in wounds grossly contaminated by soil refuse and clothes

Material—Combined antitoxin containing 2 000 units each of Clostridium perfringens and Clostridium septicum antitoxins and 1 500 units of tetanus antitoxin per vial, is prepared by the following firms

Cutter Laboratories	National Drug Co
Lederle Laboratories Inc	Parke Davis & Co
Eli Lilly and Co	E R Squibb & Sons

Methods—The contents of one prophylactic vial is given *intramuscularly* If the wound is severe and badly contaminated the dose is repeated daily as long as danger of infection exists

Contraindications are those of serum reaction

DIAGNOSIS

No immunologic method available

TREATMENT

Indications—At earliest signs of gas gangrene serum therapy is started in conjunction with chemotherapy

Materials—Therapeutic Gas Gangrene Antitoxin (derived from horse serum) is prepared in syringes and/or vials containing 10 000 units each Cl. perfringens and Cl. septicum antitoxins by

Cutter Laboratories
Eli Lilly and Co
Parke Davis & Co

Trivalent Gas Gangrene Antitoxin containing 10 000 units each of Cl perfringens and Cl. septicum antitoxins and 1 500 units of Cl. oedematiens antitoxin is prepared in vials by

E R. Squibb & Sons
Wyeth Inc

A product generally preferred because of its polyvalence and the modification of the horse serum is Polyvalent *Gas Gangrene Antitoxin* containing 10 000 units each of Cl perfringens and Cl septicum antitoxins 1 500 units each of Cl novyi and Cl bifermentans antitoxins and 3 000 units of Cl histolyticum antitoxin It is prepared in a single vial by

Lederle Laboratories Inc.

Methods—From a practical point of view it seems best to give the contents of four vials of the polyvalent serum *intravenously* and repeat at about two hour intervals until clinical improvement begins Owing to the prolonged use of serum in this disease much caution *is required to anticipate serious constitutional reactions*

Sulfadiazine penicillin and streptomycin are reported to be of value and together with antitoxin and surgery may reduce the fatality rate If surgery is indicated at any time it should be pursued to the fullest extent concomitantly with the immunologic and chemotherapeutic procedures In other words there should be no modification of indications for surgical intervention because of other previous or synchronous therapy

IMMUNITY

There is no natural immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

In civilian life reduction of the incidence of this disease depends largely on the success of antiaccident campaigns

Infantile Paralysis (Anterior Poliomyelitis)

INCUBATION PERIOD

From 4 to 20 days

PRODROMAL SYMPTOMS

Fever and headache There may be none

PROPHYLAXIS

ACTIVE IMMUNIZATION—No method of generally accepted value is available

PASSIVE IMMUNIZATION—Human poliomyelitis convalescent serum is said to be of some value It is sometimes obtainable from convalescent serum centers Injection is intramuscular and the dosage is 20–40 cc

DIAGNOSIS

No immunologic method is available Also there are no skin tests

available for ascertaining the presence or the absence of immunity

TREATMENT

Human poliomyelitis convalescent serum is said to be of some value in treatment during the preparalytic stage *Dosage is 100 cc, and some authors advise up to 300 cc* It seems worth trying in bulbar cases even if paralysis has appeared In these cases the dose is 300 cc It is given intramuscularly or intravenously *never* intra thecally Repeat the dose every 24 hours until there is definite im provement There are no dangers from the use of serum if it is not given intrathecally

When convalescent serum is not available *pooled normal adult human serum* may be of value since normal adult blood contains specific immune bodies There have also been reports of good results following transfusions with adult blood.

IMMUNITY

The most susceptible age is 5–7 years One attack confers immu nity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

The number of cases reaches its peak in the summer and early fall The risk of transmission by close respiratory contact with a patient in the late stage of the incubation period and the possibility of trans mission orally in food, milk or by swallowing water in contaminated swimming pools has recently been stressed Passage through a seasonal host or existence of a seasonal vector must also be con sidered Moreover it is considered likely that healthy carriers abor tive cases nonparalytic cases and early convalescent cases may transmit the disease

All cases should be isolated Contacts are quarantined Large gath erings should be discouraged during an epidemic

Influenza (Grip)

Influenza is caused by a characteristic virus of which immuno-logic types A and B have been differentiated. Additional variants

may exist. Complications are frequently caused by secondary bacterial invaders such as pneumococci streptococci staphylococci and Hemophilus influenzae

INCUBATION PERIOD

One to four days

PRODROMAL SYMPTOMS

Fever prostration pharyngolaryngitis

PROPHYLAXIS

A vaccine has been prepared from virus (both types A and B) grown in chick embryos which in large scale trials has proved its efficacy

Indications—Since establishment of immunity takes at least two weeks immunization will presumably come too late if employed after an epidemic has started The procedure should therefore be carried out routinely each year or at the first warning of an approaching epidemic

Material—Vaccine is supplied in 1 cc. and 10 cc vials by

Lederle Laboratories Inc
Eli Lilly and Co
Parke Davis & Co
Pitman Moore Co
E R. Squibb & Sons

Method—One dose of 1 cc is given *subcutaneously* In children it is best to give two doses of 0 5 cc each one week apart The duration of immunity is not known exactly but is presumed to be from 6 to 12 months

Contraindications—The vaccine is prepared from the allantoic fluid of chick embryos Undesirable local or generalized reactions have been observed occasionally in persons allergic to egg chicken or chicken feathers Immunization of such persons should either not be attempted or in case of necessity the dose should be further subdivided and administered under close supervision

DIAGNOSIS

No immunologic method available

TREATMENT

No immunologic method available

IMMUNITY

There is no natural immunity to this disease Immunity acquired through infection is either absent or of short duration

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Widespread use of the vaccine may become a public health measure In the meantime isolation of cases and restriction of contacts during an epidemic are the only available methods of control

Measles

INCUBATION PERIOD

Eight to 11 days

PRODROMAL SYMPTOMS

Like those of the common cold often with severe cough These and variable fever may last two or three days before the appearance of Koplik s spots or the eruption

PROPHYLAXIS

ACTIVE IMMUNIZATION —No procedure is generally available Stokes has recently reported an egg passage virus which produces a mild form of the disease and thus confers active immunity The methods of passive immunization wherein a serum modifies the course of the illness could be considered in a sense active immunization particularly when the child is deliberately exposed to infection

PASSIVE IMMUNIZATION —*Indications* —There are as a rule two objectives in immunizing persons who have been exposed to measles One is a *complete* prevention of the disease the other and more frequent a *modification* of the illness It is the present opinion that *every child under 6* and *every adult who has been exposed* and who has not previously had measles should be immunized

In an older healthy child the object is to permit a modified form of the disease to develop This is accomplished either by in

jecting a smaller amount of serum than that required for complete protection or by giving the serum a little later in the course of the incubation period.

Complete prevention by giving sufficient serum as early as possible is indicated after exposure to measles under the following circumstances

a) In infants and children under 3

b) In a child suffering from malnutrition rheumatic fever tuberculosis a nutritional disease or other debilitating or contagious disease

c) In the siblings of a child in whom complete prevention is desirable

Materials—Placental Globulin (Immune Globulin) is generally accepted as of value in preventing or modifying measles It is the most convenient material. It is supplied in 2 cc and 10 cc vials by many reputable commercial houses The following are listed in the 1946 N N R

Lederle Laboratories Inc
National Drug Co
Parke Davis & Co
Pitman Moore Co
Sharp & Dohme Inc.
E R Squibb & Sons
Wyeth Inc

A dried form with diluent to make 2 cc and 10 cc of restored serum is also made by

Sharp & Dohme Inc

An immune serum globulin (human) in 2 cc vials is prepared by

Cutter Laboratories

Measles Convalescent Serum also generally accepted has an advantage over placental globulin in that there are virtually no untoward reactions This material is listed in N.N R. 1946 and is obtainable from the convalescent serum centers

Pooled Normal Human Serum possesses enough measles antibodies to confer immunity if given in sufficient dosage If no pooled serum is available in an emergency a parent or other volunteer may be used.

Connaught Laboratories Anti Measles Serum (concentrated human, adult) in 5 cc. vials

Methods —Placental globulin extract is injected *intramuscularly* To *modify* the disease give *2 cc* during the first three days of the incubation period and *4–5 cc* after three days (Give the larger doses to older children) To *prevent* the disease *double* the doses In calculating the day of exposure one should bear in mind that the rash appears on the second to the fourth day of the disease When the rash becomes visible on the first patient the exposed person is already in his second to fourth day of incubation not in the first day

Measles convalescent serum is given *intramuscularly* To *modify* the disease give *5 cc* to a child under 3 *7 5 cc* from 3 to 7 and *15 cc* over 7 The serum should be administered during the first five days of the incubation period Later in the incubation period instead of 5 cc 10 cc should be given To *prevent* measles entirely the above specified doses should be *doubled*

Normal human serum is given *intramuscularly* in doses of 15–30 cc A convenient technic is to draw 30 cc or more of whole blood from a parent and rapidly inject half into each buttock of the child Precautions regarding the use of human blood should be considered (p 105)

In selecting and applying the above measures it is necessary to bear in mind that the child *in whom measles has been entirely prevented has immunity of only short duration and is susceptible to further attacks whereas the child who has had modified measles is usually permanently immune*

Another word of caution should be added Although an individual protected by passive immunization may not develop measles he may nevertheless develop the respiratory complications of the measles infection Contact with sources of infection should therefore be prevented *even after protection*

Contraindications —Untoward reactions to placental globulin extract occur somewhat frequently They consist of pain erythema edema malaise and some fever There are virtually no untoward reactions to the human serums

DIAGNOSIS

No immunologic method is available nor are tests for ascertaining the presence or absence of immunity to the disease

TREATMENT

In the *pre eruptive* stage placental globulin extract 10 cc *intramuscularly*, and convalescent human serum, 50 cc *intramuscularly* are generally accepted as being of some value Normal human serum 50–70 cc *intramuscularly* is generally accepted as being of *little value even in the pre eruptive stage These agents are generally of no value after the eruption has appeared*

The complications of measles are to be treated by the best available methods for treatment of the particular bacterial infections

IMMUNITY

Infants under 6 months are relatively nonsusceptible to measles Susceptibility is general in early childhood but diminishes in older groups An attack of measles usually confers permanent immunity The *duration of immunity* in a child who had measles *modified by the injection of a serum* will largely depend on the severity of the modified illness

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

The only generally accepted method of preventing the spread of measles is isolation of potential and known sources of infection. In private practice exposed siblings are usually given immune globulin or adult serum with the intention of modifying the disease In institutions injections are given with a view to complete protection

Routine injection of 20–30 cc of parental blood in every child admitted to the service is said to be of value in preventing the disease on pediatric wards

Immune contacts —persons who have recently been exposed but who have an acquired immunity to the disease—need not be segregated There are *no* measles carriers Susceptible contacts —exposed persons who possess no known immunity—are quarantined for two

weeks and should be given injections to afford partial immediate immunity

Meningitis

The most common forms of meningitis are those caused by the meningococcus the pneumococcus and the tubercle and influenza bacilli The latter two are particularly prevalent in young infants There is no known immunologic method available for the diagnosis or treatment of tuberculous meningitis the tuberculin test is of little diagnostic value In meningococcic and pneumococcic meningitis chemotherapy and penicillin have largely replaced treatment by immune serum and immune serum for treatment of pneumococcic cases is no longer available Nevertheless immunotherapy still plays a role in severe cases particularly in those caused by the influenza organism Successful treatment depends on prompt bacteriologic diagnosis The micro organism must be isolated since there is no agglutination test or skin test by which to identify the causative agent

There is no immunologic method available for the *prophylaxis* of meningitis The three main etiologic types of meningitis will be discussed separately

MENINGOCOCCIC MENINGITIS

INCUBATION PERIOD

Two to 10 days

PRODROMAL SYMPTOMS

Sometimes sore throat often hyperesthesia and headache for a day or two before the acute onset of fever and stiff neck

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

No immunologic method available

TREATMENT

Indications—Penicillin and sulfonamide drugs have largely displaced serum in the treatment of meningococcic meningitis Serum is used only in severe cases accompanied by blood stream invasion and toxicity *Antiserum is now generally given intravenously* and rarely administered intrathecally

Material—Antimeningococcic Serum Concentrated and Refined is used (10 cc. is equivalent to 40 cc. of the unconcentrated serum.)

National Drug Co 10 cc. double end cylinders for intraspinal or intravenous injection.

Method—Meningococcus antiserum prepared by immunizing animals against the several types of the organism is generally accepted as of value in treatment on the infrequent occasion when chemotherapy alone seems not sufficient for the apparent severity of the infection

Intravenous injection is more and more supplanting the intrathecal route The dose is large up to a total of 600 cc being used The serum may be administered through the continuous intravenous infusion apparatus used for the sulfonamide

If the intrathecal route is used at least 30 cc of concentrated serum should be given at the first spinal tap after an equivalent amount of spinal fluid has been withdrawn Repeat every 8–12 hours to a total dosage of 150 cc in moderately severe or 300 cc in severe cases Termination of treatment is indicated by the clinical picture the disappearance of micro-organisms from the spinal fluid a clearing of the fluid or a rise in glucose level from that usually found in the acute case Treatment with serum over too long a time should be guarded against In recurrences serum should be given only with the greatest caution Sometimes owing to serum reaction there is a recurrence of symptoms and spinal fluid changes (except the appearance of organisms) *This possibility should be considered* before further serum treatment of an exacerbation is started Serum treatment should cease at the appearance of a serum rash

Contraindications—When the antiserum is used the usual pre cautions regarding horse serum hypersensitivity must be taken

IMMUNITY

There is no natural immunity to the disease

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Transmission is from person to person by direct respiratory con tact The *carrier* is more important than the sick case So far as *epidemic* meningococcic meningitis is concerned the problem is the *identification of the carrier* A control procedure more easily carried out and for practical purposes more desirable is treatment of the entire group endangered with sulfadiazine (1 Gm daily for adults) This method has proved of great value in Army and Navy camps The disease is not transmitted by food or drink

PNEUMOCOCCIC MENINGITIS

INCUBATION PERIOD

Not known exactly for the meningitis is usually secondary to trauma otitic infection or pneumonia

PRODROMAL SYMPTOMS

Onset of headache vomiting and spinal stiffness after trauma or during otitic infection or pneumonia

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

No immunologic method available

TREATMENT

No immunologic method is available The sulfonamides and penicillin are effective in some cases

INFLUENZAL MENINGITIS

INCUBATION PERIOD

Varies Onset may be acute or very gradual

PRODROMAL SYMPTOMS

Vary from acute onset to gradual onset over several days In young infants there may be only low grade fever for weeks

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

No skin test or other office immunologic method available

TREATMENT

Indications—In all cases of influenzal meningitis the generally accepted treatment is sulfadiazine plus Alexander s anti influenzal rabbit serum The sulfonamide is started at once by continuous intra venous infusion. About 3–4 hours later the specific serum is ad ministered. This may be given intrathecally or intravenously the latter rapidly becoming the route of choice Results by the intra venous route are good and the method is much simpler than the one requiring repeated spinal punctures Continuation of antiserum ad ministration is guided by the patient s response

Materials—Anti Haemophilus Influenzae Type B Serum, Rabbit (H E Alexander) is prepared by

E R Squibb & Sons vials containing 25 mg. agglutinin antibody nitrogen equivalent to not less than 25 000 pro visional units

Diagnostic Serum for the Capsular Swelling Test Type B is pack aged in boxes of three capillary tubes by Squibb Similar serum for type A, used during treatment to determine adequacy of serum dosage is procurable on special order

Method—After the intravenous infusion of the sulfonamide has been continued for four hours administer intrathecally one vial of the influenza antiserum (containing 25 mg antibody nitrogen) Then give additional antiserum intravenously for two hours in doses of 50 mg antibody nitrogen for an average case and 75 mg for cases with severe infection Adequacy of dosage is checked one hour later by testing the ability of the patient s serum to produce capsular

swelling of the influenza micro-organism with which he is infected (Neufeld phenomenon) If there is no Neufeld phenomenon the dose is repeated The specimen of the patient s spinal fluid with drawn before treatment serves as a source of micro organisms for the Neufeld reaction If it has enough micro organisms 0 4 per cent formalin is added and it is stored in the refrigerator removed only for a few minutes daily to obtain a specimen for use Further treat ment is gaged by results of spinal fluid smears and cultures and by determinations of its sugar chloride and protein content

Antiserum given by the *intravenous route only* has proved so ef ficacious that the preliminary intrathecal dose is gradually being discarded If administered only intravenously a minimum of 100 mg antibody nitrogen should be used initially Again the Neufeld test should be done in one hour

Contraindications —The usual precautions against serum reaction must be taken

Mumps (Epidemic Parotitis)

INCUBATION PERIOD

One to three weeks

PRODROMAL SYMPTOMS

Perhaps a tingling of mouth sharpening of taste and dysphagia frequently severe pain in the ear on the affected side

PROPHYLAXIS

Mumps convalescent serum (20 cc) injected *intramuscularly* is said to be of value It is particularly indicated when an adolescent has been exposed It is also indicated in an outbreak at a camp or institution Since many adults are susceptible to mumps and par ticularly since *orchitis* or *oophoritis* is a complication in adults in jection of *parents or other exposed adults* should be considered The serum should be given early The immunity conferred is of short duration and the injection must be *repeated after every exposure* Convalescent serum centers supply this serum

DIAGNOSIS

No immunologic method for office use is available

TREATMENT

Mumps convalescent human serum injected *intramuscularly* in 40 cc doses is said to reduce the incidence of orchitis and oophoritis It is especially indicated in adolescents and adults suffering from the disease It is of no value after complications have developed

IMMUNITY

One attack usually but not always confers immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

The disease is transmissible from two days before the swelling appears to after its subsidence Isolation should continue for three weeks from onset The disease is not carrier borne

Plague

INCUBATION PERIOD

Three to 4 days occasionally as long as 14 days in primary pul monary plague from 2 to 3 days

PROPHYLAXIS

ACTIVE IMMUNIZATION —*Indications* —Active immunization with plague vaccine is thought to be of considerable value Immunize persons living or traveling in areas in which plague is encountered and laboratory personnel working with the micro organism

Material

Cutter Laboratories vaccine of 2 000 million micro-organisms per cc, in vials of 20 cc

Method —A first dose of 0 5 cc of the vaccine is given *subcutaneously* followed 7–10 days later by a second dose of 1 cc A booster dose of 1 cc is given every four to six months for as long as danger of exposure to plague exists

Duration of immunity induced by vaccine is uncertain It seems likely that the vaccine at least modifies the severity of the disease

even if it fails to prevent it (The evidence of induced immunity is based largely on the observations of protection in mice and on the demonstration of antibodies in human beings)

Contraindications —None

DIAGNOSIS

No immunologic method available

TREATMENT

Antiplague serum has been used experimentally but it is not generally available Moreover it is thought to be no more efficacious than chemotherapy (sulfadiazine) although a combination of the two might be advantageous

IMMUNITY

From clinical experience it is known that plague may leave immunity in survivors although nothing is known about the duration of the immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

The reservoir of plague is the rodent population particularly rats the infection is transferred from the rodent to man by fleas Public health measures therefore necessarily concentrate on interruption of the chain rodent—flea—man

Plague is endemic among many rodents including ground squirrels in the western half of the United States This endemic (animal) infestation is often referred to as sylvatic plague It constitutes an ever present menace Under normal conditions infection is carried to man only occasionally through contacts with these wild rodents for instance in hunters

Pneumonia

INCUBATION PERIOD

Not uniform but usually one to four days

PRODROMAL SYMPTOMS

Symptoms of an upper respiratory infection usually with persistent cough

PROPHYLAXIS

No generally accepted immunologic method is available The use of pneumococcus vaccine is not generally accepted as of value

DIAGNOSIS

There is no simple immunologic test which will help in the diagnosis of pneumonia. In an occasional case enough microorganisms are present in the sputum to give a visible quellung phenomenon (swelling of capsule) when group or individual typing serums are mixed on a slide with sputum Typing of the microorganism is of theoretical interest only for therapeutic serums are no longer available

TREATMENT

The use of penicillin and of sulfonamide drugs now so far overshadows treatment with specific serum that the latter is no longer manufactured

IMMUNITY

Allergic sensitization plays an important role in the pathogenesis of pneumonia Protective antibodies regularly develop after injection of vaccines but it is not known how long this protection lasts and of course relapses do occur Moreover even temporary immunity is *type* specific and pneumococcal disease from other types of pneumococci may develop This makes it even more difficult to judge immunity after exposure

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Transmission is by respiratory contact with a case Isolate In large groups Felton s carbohydrate antigen may be of prophylactic value if available from the U S Public Health Service During an epidemic small daily doses of a sulfonamide or penicillin may be of prophylactic value if the strain of pneumococcus is susceptible The family of a patient with pneumonia usually has a high incidence of carriers

even if it fails to prevent it. (The evidence of induced immunity is based largely on the observations of protection in mice and on the demonstration of antibodies in human beings)

Contraindications —None

DIAGNOSIS

No immunologic method available

TREATMENT

Antiplague serum has been used experimentally but it is not generally available Moreover it is thought to be no more efficacious than chemotherapy (sulfadiazine) although a combination of the two might be advantageous

IMMUNITY

From clinical experience it is known that plague may leave immunity in survivors although nothing is known about the duration of the immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

The reservoir of plague is the rodent population particularly rats the infection is transferred from the rodent to man by fleas Public health measures therefore necessarily concentrate on interruption of the chain rodent—flea—man

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Pneumonia

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a diagnosis of rabies and is *no indication to stop injections* if there is any cause for suspicion The decision is often difficult.

The immediate prophylactic treatment for any animal bite is cauterization with fuming nitric acid The wound or wounds should be ringed with vaseline and the nitric acid dropped on the wound with a pipette The acid should not be neutralized

Materials—There are two general types of rabies vaccine available Rabies Vaccine (Semple) is considered of most value In this vaccine virus in brain and cord tissue of inoculated animals is killed by suspen sion in phenol the material then suspended in physiologic saline solu tion and standardized in mice Each dose is contained in a separate vial These are packaged in units of 7 and 14 vials by

Cutter Laboratories	Sharp & Dohme Inc
Lederle Laboratories Inc	E R Squibb & Sons
Medical Arts Laboratory	Terrell s Laboratories
National Drug Co	U S Standard Products Co
Pitman Moore Co	

The following companies also package each dose in a syringe ready for use

National Drug Co	U S Standard Products Co
Sharp & Dohme Inc.	Wyeth Inc.
E R Squibb & Sons	

Rabies Vaccine (Harris) is made by freezing the infected tissue and drying rapidly It is then placed in sealed tubes and accompanied with vials of physiologic saline

D L Harris Laboratory Metropolitan Building, St. Louis series of 10 consecutive doses

Eli Lilly and Co series of 14 consecutive doses

The packages are accompanied by a syringe for use in the injections Most firms making rabies vaccine will send it to the patient by the fast est delivery possible

Method—In *head and neck* bites and in extensive bites and lacerations elsewhere *21* injections are given two injections a day for the first seven days and one daily for seven days more

In bites more distant from the central nervous system in bites through clothing which are immediately followed by cauterization and in cases in which abrasions are merely contaminated with the animal saliva 14 injections are given one a day for two weeks *All injections are given subcutaneously, in the abdominal and intra scapular areas Don t massage the area after injection* The treatment is by no means always successful but it is generally of great value (*Start immediately* Telephone or telegraph the nearest company for *rapid service* or consult the local health officer)

Contraindications —Paralysis of unknown cause is a rare compli cation of the vaccine injections After several doses there may be local induration around each injection but this is no contraindication to continuing the injections

DIAGNOSIS

No immunologic method available

TREATMENT

No immunologic method available

IMMUNITY

There is no lasting natural immunity Immunity after inoculation lasts only about six months Exposure after that period therefore indicates a new course of treatment

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Public health methods of control include the reporting of every dog bite and the incarceration and observation of all reported dogs Although rabies is most frequently encountered in dogs it is also found in cats in other felines such as foxes and in cattle horses swine wolves and coyotes

Strict quarantining of dogs before entry into the country has kept the disease out of Australia Hawaii and the British Islands Muzzling of dogs at all times and muzzling and restraint of all dogs during epidemics are essential Vaccination of all dogs will also result in virtual elimination of the disease

Rheumatic Fever

There are no *generally* accepted immunologic office procedur for the prophylaxis diagnosis or treatment of rheumatic fever

Rocky Mountain Spotted Fever (Spotted Fever)

INCUBATION PERIOD

Two to five days but may be as long as 14 days

PRODROMAL SYMPTOMS

Acute onset with fever chills pains and rash

PROPHYLAXIS

ACTIVE IMMUNIZATION —*Indications* —The vaccine is usef in persons living and/or working in tick infested areas and in lab ratory workers Vaccination however is necessary each year It shou be pointed out that the incidence of infection is low considering t high incidence of tick bites Also it is well to remember that ev with the high efficacy of the vaccine the best prophylactic measu are protection of the body with adequate clothing use of chemic repellent agents and careful removal of the tick

Material —Vaccine made from ground up tick material or fr culture grown on the yolk sac of chick embryo i prepared by

U S Public Health Service	Sharp & Dohme Inc
Several state laboratories	Wyeth Inc
Lederle Laboratories Inc	

The chick embryo vaccine is considered to be somewhat superior the tick material.

Method —Two doses of *2 cc* each are given *subcutaneously* week apart the second dose should precede the local tick season six weeks The vaccine will give full or partial protection for o season A booster dose of 1 cc is given annually about six wee before the onset of the tick season The disease in immunized perso is likely to be mild

Contraindications—Occasionally local reactions (erythema swell ing pain) occur but are of no consequence When vaccine prepared from the yolk sac of chick embryos is used undesirable local or generalized reactions have been observed clinically but fortunately rarely in persons allergic to egg chicken or chicken feathers Im munization of such persons either should not be attempted or in case of necessity the dose should be further subdivided and adminis tered under close supervision

DIAGNOSIS

No immunologic method available

TREATMENT

Indications—Although there is little published evidence avail able it would appear that immune serum may be of considerable value The serum must be used early in the prodromal period or at the latest before the third day of the eruption

Material—Immune Rabbit Serum may be obtained from the fol lowing pharmaceutical houses in vials of 20 cc

Lederle Laboratories Inc.
Sharp & Dohme Inc
Wyeth Inc

Method—After testing for rabbit serum sensitivity three or four doses of 20 cc each are given *intramuscularly* within 36 or 48 hours Continued serum therapy then depends on the condition of the patient

Contraindications—The usual precautions against reactions due to serum sensitivity must be taken

IMMUNITY

Clinical infection leaves a long lasting and possibly permanent immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Ticks (Dermatocentor andersoni) carry the infection from man to man and also serve as a reservoir of infection. Guarding against tick bites is therefore the most important health measure in regions where

the disease is endemic It is important to know that foci of spotted fever have recently been discovered far beyond the region where the disease was first observed (e g in Long Island N Y and around Washington D C)

Scarlet Fever (Scarlatina)

INCUBATION PERIOD

One to five days

PRODROMAL SYMPTOMS

Fever headache sore throat vomiting generalized aches and pains for one to two days before the rash

PROPHYLAXIS

ACTIVE IMMUNIZATION —*Indications* —Until recently active immunization against scarlet fever with unmodified toxin was not widely practiced because the method was awkward and the incidence of serious reactions was high. Recently a toxoid prepared by the method of M V Veldee of the U S Public Health Service has over come most of these objections By Veldee s method the toxoid is pre cipitated with tannic acid and resuspended in aluminum hydroxide giving a relatively harmless but highly antigenic product Active im munization is indicated

a) In susceptible patients attendants nurses and doctors at con tagious disease hospitals

b) In susceptible inmates of children s homes

c) In institutional epidemics A few injections given children with positive Dick tests may abate the spread of the epidemic

d) It is sometimes but not generally carried out as a routine pro- cedure in infants 12–18 months of age

e) It is perhaps of some value even *after* exposure to the disease

Materials —Scarlet Fever Streptococcus Toxin, Tannic Acid Precipi tated and Aluminum Hydroxide Resuspended is packaged for 1 immu nization and for 10 immunizations for children, 1 and 10 immunizations

for adults and 1 and 10 supplementary injections for both children and adults and is supplied by

Lederle Laboratories Inc
Wyeth Inc

Scarlet Fever Streptococcus Toxin is supplied by many reputable houses for those who wish to use it and is packaged in sets of five vials each vial containing a dilution suitable for each of *five injections* In the large sized set each vial contains 10 cc. of diluted toxin, so that the set is used to immunize 10 children Smaller sets for immunization of one child contain 1 cc. vials of the proper dilution of toxin. In addition these houses supply a 1 cc package containing 100 000–120 000 skin test doses which is used if the *Dick test is still positive after the regular series of five injections* The toxin is available from

National Drug Co	E R Squibb & Sons
Parke Davis & Co	U S Standard Products Co
Sharp & Dohme Inc	

Methods —The toxin treated according to the method of Veldee is injected *intracutaneously* at two week intervals as follows in children 750 3 000 and 10 000 skin test units in adults 500 2 000 6 000 and 10 000 skin test units The vials are so prepared that the dose for each injection is contained in 0 1 cc of solution If the Dick test is found to be positive after two months a supplementary injection of 10 000 skin test units is given

The scarlet fever streptococcus toxin given in *five subcutaneous injections* is given at *weekly intervals* Each injection of toxin consists of 1 cc but the dilution varies so that the first injection contains 162–650 skin test doses and succeeding injections are increased to 2 500 10 000 30 000 and 120 000 units respectively About 90 per cent of susceptible individuals so treated develop negative Dick tests and do not develop scarlet fever despite repeated intimate contact Immunity by this method appears in a few weeks and is said to last up to 10 years although it may last even less than 2 years If an injection of antitoxin has been given 10 days should elapse before active immunization with toxin can be started

The disadvantages of immunization are

1 Frequent failure to reverse the Dick test.

2 The great number of injections necessary

3 High incidence of untoward reactions

4 Questionable immunity to more than the *skin element in streptococcic infection*

It must be emphasized here that the immunity gained by injections of Dick toxin does *not prevent infection and invasion by the streptococcus* Toxin injection is thought by some to prevent only the eruption

Oral administration of enteric coated pills containing toxin has been favorably reported by the Dicks but it is not generally accepted as of value[3]

Contraindications—Use of the Veldee material results in few untoward reactions Reactions during active immunization with the unmodified type of toxin particularly in older children and in adults are *frequent* and sometimes *severe* and thus must be carefully weighed before immunizing an individual Reactions consist of scarlatiniform eruptions edema adenitis arthritis malaise sometimes nausea and vomiting and occasionally fever In about 1 per cent of patients reactions are severe enough to necessitate discontinuance of injections

The toxin is of course not given for the treatment of scarlet fever Before immunization a recently exposed person should be observed first for signs of the illness

PASSIVE IMMUNIZATION —*Indications*

a) In a child with a *positive* Dick test who has been in intimate *contact* with a case of scarlet fever In private practice one must weigh the relatively limited contagiousness of the disease and the

Many of the discrepancies and failures from the use of toxin and antitoxin may be explained by the theory that scarlet fever is only in part due to toxin effects and is in part attributable to sensitization and reaction to the allergenic fractions of the streptococcus

mildness of the usual case against the 10 per cent incidence of reactions to passive immunization

b) In a group of institutionalized children with positive Dick tests who have had contact with a case

Materials—Scarlet Fever Streptococcus Antitoxin is generally accepted as of value in *prophylaxis* against scarlet fever For sources of materials see page 155

Human Scarlet Fever Convalescent Serum is generally accepted as of value in *prophylaxis* The convalescent serum centers supply this material

Methods—Antitoxin *Inject 3 000 units intramuscularly as soon as possible after exposure* and *after* testing for sensitivity If there is any indication of possible horse serum sensitivity use human convalescent serum Duration of immunity is 10–14 days

Convalescent Serum Inject *intramuscularly as soon as possible after exposure* Up to 5 years of age the dose is 10 cc, from 6 to 12 years 20 cc

Contraindications—The usual precautions against reactions due to foreign serum sensitivity must be taken when using antitoxin If the patient gives indications of sensitivity use human convalescent serum There is rarely any danger in the administration of human convalescent serum If human serum is not available and there are strict indications for giving antitoxin follow the directions for avoidance or reduction of reactions (p 93)

DIAGNOSIS

DICK TEST—The Dick test is used for determination of susceptibility

Indications

a) To screen out naturally immune persons before starting active or passive immunization on institutionalization or in an epidemic

b) In clinical diagnosis Theoretically the test should be positive in the early stages of the disease and become negative after one to two weeks *Thus a positive test in the presence of fever* and a suspicious rash is only presumptive evidence of scarlet fever

Material—Scarlet Fever Streptococcus Toxin for Dick Test is put up by many reliable commercial houses in 2 cc. ampules and 11 cc vials for 5 and 50 tests respectively Those listed in N.N R. for 1946 are

Lederle Laboratories Inc	E R. Squibb & Sons
National Drug Co	U S Standard Products Co
Parke Davis & Co	Wyeth Inc
Sharp & Dohme Inc	

Method—The test is performed by the *intracutaneous* injection of exactly 0 1 cc of a dilution of toxin containing *1 skin test unit* The glass syringe should be boiled in distilled water before it is used for this purpose All vials of testing toxin contain 1 extra cc which must be used for rinsing the syringe When different needles are used for each test in a series each is rinsed by expelling 0 1 cc of the toxin through it Alcohol sterilization of needles or syringe may precipitate the toxin The test is best performed on the volar aspect of either forearm

The test site is examined in 20–24 hours An area of any degree of *redness* which extends *1 cm or more* in diameter constitutes a *positive reaction* Unlike the Schick test there is *no induration* in a positive test. *Any degree* of redness *even if faint if it is the required size* constitutes a *positive reaction* The positive reaction begins to fade after 24 hours and usually disappears in 48–72 hours If the reaction *disappears completely* within 24 hours the reaction is to be regarded as negative

The Dick test is a test for susceptibility of the skin to scarlet fever streptococcus toxin A positive reaction is generally interpreted as indicating such susceptibility A negative result is presumptive evidence of immunity to the toxin and hence to the disease or at least to the dermatotropic or erythrogenic element in the disease Although there are exceptions to this rule the test has a degree of trustworthiness warranting its continued use

The incidence of *negative tests* in the general population is low at 6 months of age and increases from *30 per cent* at 1 year to about

70 per cent at 12 years Age is a more important factor in raising the incidence of negative tests than is the fact of having had the clinical disease for many patients in the sixth week of convalescence from scarlet fever still react positively to the toxin. Active immunization produces a change from positive to negative reactions in about 90–95 per cent of cases This negative reaction is retained for two to three years It is often questioned however whether the negative reaction so acquired indicates resistance to infection.

BLANCHING TEST FOR DIFFERENTIAL DIAGNOSIS—*Indications*—A positive reaction (blanching) in 4–24 hours in a suspicious rash supports a diagnosis of scarlet fever

Materials—Scarlet Fever Streptococcus Antitoxin is put up for this purpose in 1 cc vials (5 tests) by the following concerns

National Drug Co	Sharp & Dohme Inc.
Parke Davis & Co	E R. Squibb & Sons

The antitoxin is preferable to the human convalescent serum for this purpose because of its constant content of antitoxin units, provided the patient is definitely not sensitive to horse serum. Human convalescent scarlet fever serum may however be used.

Methods—Inject *0 2 cc of the antitoxin intracutaneously* into an area of scarlatinal rash. This amount contains 600 neutralizing units. Examine every two hours for blanching *The test is not reliable after the rash is three days old* In using convalescent serum inject 0 5 cc

A positive reaction i.e appearance of blanching in 4–24 hours is evidence in favor of a diagnosis of scarlet fever A negative test i.e., no blanching is equivocal

Contraindications—The usual precautions against serum sensitivity must be taken if antitoxin is used for the blanching test. Even 0 5 cc. of antitoxin may be harmful in a patient sensitive to horse serum.

TREATMENT

Indications—Treatment with antitoxin or convalescent serum is indicated in every patient with scarlet fever who shows evidence of marked toxicity or has a temperature of 102 F or over Such trea-

ment always gives prompt relief from these toxic signs However not serum therapy alone but the combination of serum or antitoxin with penicillin or sulfonamides is the generally accepted treatment for reducing incidence and severity of complications

The human convalescent serum is especially useful in patients sensitive to horse serum Otherwise it is generally of less value in treatment than the horse serum antitoxin and because of the lower concentration of antibodies larger amounts are needed

Materials—*Scarlet Fever Streptococcus Antitoxin is supplied by many* reputable pharmaceutical houses in vials or ready to use syringes con taining 3 000 (for prophylaxis only) and 9 000 units Those listed in N.N.R. 1946 are

In vials	In syringes
Lederle Laboratories Inc.	*National Drug Co*
Parke Davis & Co	E R. Squibb & Sons

Lederle and Parke Davis serums are prepared by enzymatic digestion and are particularly refined despeciated and concentrated. Scarlet Fever Human Convalescent Serum is obtainable from the serum centers

Methods—Antitoxin First test the patient for horse serum sen sitivity and *carefully investigate the history for presence of atopy* (p 253) Then when permissible inject *intramuscularly* into the buttocks as early as possible 9 000–18 000 units of antitoxin the dosage depending on the severity of the disease Repeat the injection if there is no definite improvement in 24 hours In very toxic cases repeat the dose in 8–12 hours In more severely toxic cases the serum may be given *intravenously* Antitoxin therapy should be accom panied by adequate doses of penicillin or sulfonamides

Convalescent Serum Use particularly in atopic or otherwise sen sitive individuals Give *intravenously* In children up to 5 years the dose is 20 cc from 5 to 10 years 40 cc from 10 to 15 60 cc and over 15 80–100 cc A single dose is usually sufficient but if toxic symptoms persist repeat the dose in 24–48 hours

Contraindications—Even with the use of concentrated or de speciated antitoxin about 10 per cent of patients develop untoward

reactions Every attempt should be made to ascertain the existence of atopy and of sensitivity to horse serum If there is any evidence of such use *human convalescent serum* For symptoms of foreign serum sensitivity and the methods of preventing or reducing reactions see page 90 There are usually no untoward reactions from human convalescent serum

IMMUNITY

The incidence of scarlet fever is highest in winter Second attacks of scarlet fever are not uncommon and even third attacks have been reported Occasionally a relapse may occur during convalescence but today this is believed due to sensitivity to absorbed protein of the dead micro organisms rather than to reinfection

Active immunization with toxin gives negative Dick tests and im munity—at least to the *scarlet rash*—in a high percentage of persons However they are often susceptible to streptococcic infections

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

All cases are due to contagion from other active cases Patients are to be *quarantined for three weeks* and thereafter *until all purulent discharges have cleared up* Regulations however may vary in dif ferent localities Dick test positive contacts are isolated for a week.

Culture of the throats of contacts is not of immediate diagnostic value Active general immunization of large groups of individuals is not a method of generally accepted value However such active im munization or injections of antitoxin are indicated in *institutional epidemics*

Transmission is usually by direct respiratory exposure Milk and food may serve as disease carriers

Smallpox (Variola)

INCUBATION PERIOD

Nine to 15 days

PRODROMAL SYMPTOMS

Chills often convulsions fever headache and vomiting

PROPHYLAXIS

Active immunization by deliberately producing infection by cutaneous inoculation with cowpox virus reduces the incidence of this disease

Indications

a) In *every infant* during the first 6 months of life preferably some time between the falling-off of the cord and age 3 months

b) In *every child* during the early school years

c) In *every person* during a smallpox epidemic or threat of one

d) In *every person* going into an area where smallpox is endemic It should be noted that state laws vary greatly in attitude toward vaccination.

Materials—The *calf lymph virus* is the generally accepted agent for use in vaccinating It is supplied by most pharmaceutical firms and by departments of health In private practice kits containing individual capillaries for each patient are the most practical of the available packages

Smallpox Vaccine in boxes containing 1 5 and 10 capillary tubes for a corresponding number of vaccinations is available from many boards of health and is supplied by

Cutter Laboratories	Parke Davis & Co
Lederle Laboratories Inc	E R. Squibb & Sons
National Drug Co	

Thomas M Rivers chick embryo culture virus which is also said to be of value and to possess advantages is not yet generally available It is of utmost importance that all types of vaccine virus be kept refrigerated at all times

Methods—The choice of a site for vaccination is usually the outer aspect of the arm a little below or above the insertion of the deltoid muscle Often the proximal outer aspect of the thigh is used The proximal outer aspect of the calf of the leg is also a convenient spot The old fashioned large disfiguring scar is not obligatory no matter which location is chosen A large scar is often caused by secondary infection

There are two technics for vaccination which are desirable from a practicable and cosmetic point of view (1) multiple puncture method and (2) scratch method The former has the most authoritative approval A third method the intracutaneous is newer and may be used under certain conditions although it is not indicated for general use

Multiple Puncture Method We strongly recommend this method The child is held firmly but not necessarily motionless while the area to be vaccinated is cleansed with acetone or carbon tetrachloride A droplet of vaccine is deposited on the area and then the sharp end of the sterile needle is brought down through it to strike the skin firmly The needle point does not extend beyond the most superficial layers of the epithelium Repeat the light tap with the needle point rapidly 30–40 times Hold the arm or thigh for a minute or so until the vaccine dries If drying is slow the excess can be wiped off with sterile gauze No dressing is needed

Scratch Method. This is not as satisfactory as multiple puncture It is more apt to be painful and often causes bleeding which washes out the vaccine The technic of application of the droplet is the same but instead of multiple punctures the needle point is used to make a superficial scratch about 1 cm in length through the drop and the virus is then rubbed in with the flat of the needle

Intracutaneous Method This is a relatively new method and although it promises to be of value is not yet generally accepted It may be used with calf lymph virus Take up the contents of a capillary tube into a hypodermic needle drawing up through it 0.2 cc physiologic saline solution into a tuberculin syringe The area is cleansed as before Inject intracutaneously slowly (the material is viscid) 0 1 cc of the *diluted* virus The injection should raise a white slightly elevated wheal Cleanse the surface needle puncture with acetone By this method an occult take may occur without leaving a scar

It is generally conceded that no close constricting or impervious dressing should be used to protect a vaccination We prefer only a dressing such as a band aid, loosely applied for 12 hours following the vaccination When the reaction is at its height a piece of sterile gauze sewn on the inside of the patient s shirt sleeve is all that is necessary

N B It cannot be too strongly emphasized that there is real danger of serious complications in vaccinating persons with open skin lesions, eye lesions or pruritus The dissemination of the virus can lead to widespread or generalized vaccinia (p 160)

Description of Local Reactions —There are several types of reactions to the vaccination with calf lymph virus

1 Primary Take This occurs in patients who have no immunity to smallpox—i.e in those who have never had smallpox or cowpox or been successfully vaccinated and in those whose acquired immunity from previous vaccination or from smallpox or cowpox is no longer present In two to four days a tiny papule surrounded by erythema appears at the point of inoculation One or two days later the tip of the papule vesiculates By the seventh or eighth day the vesicle has grown considerably and the area of erythema has also extended greatly On the tenth day the lesion begins to dry out and the inflammation begins to subside At 15–18 days the vesicle becomes a crust and this falls off at about 21 days The scar at first is pink and pitted but over a period of weeks it generally blanches and becomes smooth

At the height of the reaction the patient often has a mild temperature some irritability and considerable pain in the arm These symptoms usually respond well to acetyl salicylic acid

2 Accelerated Take (Vaccinoid Reaction) If the patient possesses some degree of immunity usually from previous vaccination the reaction will be the same as described but the stages will be less intense and will follow one another and progress more rapidly The vesicular and inflammatory reaction is smaller the constitutional

symptoms are slight and the entire reaction is over in about 10 days (compared with about 21 days for the primary take)

3 Reaction of Immunity A papule develops before 24 hours and subsides within three days Provided there was proper vaccination technic with a virus known to be potent this means the patient en joys full immunity

If none of these three develops there is something wrong with the virus or with the technic The vaccination must be repeated

4 Primary Take Reaction to Intracutaneous Technic If the intra cutaneous technic is used the blanched wheal disappears in about 12 hours In a day or two a small area of erythema and induration ap pears which becomes larger until it is 1 5–3 cm in diameter At this time there also is a central raised papule After 8–10 days there is a gradual recession and at two weeks all that is left is a faded erythema tous pigmented area showing slight desquamation and surround ing a tiny papule General symptoms are unusual and if they do occur are mild

Contraindications —In debilitated children a slough may develop at the vaccination site A patient with atopic dermatitis or other itch ing skin condition or with itching or other condition of the eye or one in contact with siblings or others with such dermatoses or eye disease *should not be vaccinated* Such patients or contacts may de velop a severe smallpox like vaccinia with scarring or a serious gen eralized vaccinia

Keratitis with scarring and permanent visual impairment is an other dreaded consequence Dermatologists and others who handle patients with itching or other diseases of the skin and eye must take the utmost precautions for destroying or removing all traces of virus from hands clothing and equipment and must carefully destroy all packages and materials used To prevent the virus from contaminat ing objects and equipment throughout dermatologic and ophthalmo logic offices and clinics when possible one room should be reserved for vaccination

It is noteworthy that in the presence of open or itching or inflam matory dermatoses all these precautions may not prevent vaccinia For the generalization of the virus is not necessarily due to external inoculation Vaccinia also occurs when the virus is disseminated hematogenously and localized in the open or irritated skin areas (isomorphic reaction)

Existence of an acute illness is no contraindication to vaccination during a threatened epidemic Most patients develop a moderate tem perature rise but sometimes the elevation may go to 104 F or over Treatment with salicylates is indicated

In some cases a cellulitis develops which occasionally becomes extensive and severe It must then be treated as such (immobilization penicillin sulfonamides compresses)

Tetanus is another serious but fortunately extremely infrequent complication Reliable virus good skin sterilization and avoidance of close covering of the lesion will reduce this possibility

Erysipelas impetigo and scarlet fever have been reported follow ing vaccination Rashes of various sorts resembling roseola toxic erythema and even urticaria occasionally occur on the ninth to the twelfth day They are not serious

The specific action of vaccination probably affects all tissues but particularly the ectodermal ones such as the skin and nerve tissues Polyradiculitis neuritis and particularly encephalitis have been re ported following vaccination These complications usually occur at the height of the local cutaneous reaction They are rare in vac cination during early infancy *This is another reason for early vaccination*

There is no generally accepted treatment for generalized vaccinia or postvaccinial encephalitis However injection of 10–20 cc *human vaccinial convalescent serum* is said to be of some value in modify ing the course of a severe vaccination reaction and in larger doses if obtainable might be of some value in these other complications

DIAGNOSIS

No immunologic method available

TREATMENT

There is no immunologic method of value Vaccination during the early stages of the disease may exert a favorable influence on its course

IMMUNITY

Susceptibility to smallpox is universal or nearly so There is no proof of acquisition of immunity from subclinical exposures

Under present conditions in this country vaccination should be repeated every 5–8 years but in the face of an epidemic immediate revaccination is strongly advised

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Vaccination against smallpox is generally accepted as a must in all public health programs Transmission is by contact with a patient Carriers i e persons not having smallpox play no role in transmitting the disease *There is no evidence that food or drink carry the infection*

Staphylococcic Infections

Infections caused by staphylococci fall into two large clinical groups localized and generalized infections The former may be amenable to some forms of immunologic treatment For treatment of the latter group we must rely chiefly on sulfonamides and penicillin The known antigens of the staphylococcus organisms consist of soluble toxins (leukocidin hemolysin, a tissue necrotizing agent) plasma coagulase and body antigens or allergens Immunologic agents considered of some use in combating localized infections include vaccine consisting of bacterial bodies toxoids and antitoxin

INCUBATION PERIOD

Generally not ascertainable

PROPHYLAXIS

No immunologic prophylactic measure in the strict sense of the word (See treatment.)

DIAGNOSIS

No immunologic method available

TREATMENT

Indications—Toxoid stock vaccine and autogenous vaccine are of some value in treating selected cases of staphylococcic infections particularly in prophylactic treatment of recurrent staphylococcic infections of the skin (p 363) and of the eyes (conjunctivitis blepharitis etc) These measures are designed to restore the normal resistance of the body to staphylococci However the severity of a staphylococcic infection depends not only on the resistance of the host but also on the virulence of the micro-organisms which varies greatly

Staphylococcus antitoxin is said to be of some value in the treatment of acute local or generalized highly virulent infections The usefulness of antitoxin is greatly reduced by the vast therapeutic superiority of the antibiotic and chemotherapeutic agents

Materials—The sources for stock vaccine autogenous vaccine and toxoid are listed under staphylodermas Staphylococcus Antitoxin in vials containing 10 000 I U is supplied by

E. R. Squibb & Sons

Methods—The uses of vaccines and toxoid are described for staphylodermas (p 365)

Antitoxin treatment may be started with 10 000 units in localized infections For severe or generalized infections 50 000–100 000 units should be the starting dose Continue daily until clinical improvement is seen Treatment is usually *intramuscular* but antitoxin may be given intravenously in urgent cases It should be given early in the disease

Contraindications—Those for vaccines and toxoid are described for staphylodermas With antitoxin the usual precautions must be taken against the untoward effects of foreign serum

IMMUNITY

Human beings normally have a fair degree of resistance to staphylococcic infection except to occasional strains of high virulence Chronic or recurrent infection with staphylococci of low virulence is evidently conditioned by some disturbance of the normal local or general resistance of the body and recovery depends on the restoration of this resistance It is on this basis that therapeutic effect of treatment with vaccine or toxoid must be explained However no reliable method is available for gaging the degree of resistance Exhaustive disease and metabolic disturbances such as diabetes tend to lower the general resistance Beyond that it is obvious that general cleanliness is most important for protection against staphylococcic infection This is particularly true in wounds where the staphylococcus is an important member of the variegated group of secondary invaders

Tetanus (Lockjaw)

INCUBATION PERIOD

Usually four days to three weeks the incubation period may be as long as three months or more The bacilli can remain quiescent in the injured tissue for many months making it difficult to ascertain when danger of infection is passed

PROPHYLAXIS

Both active and passive immunization are generally conceded to be of great value

ACTIVE IMMUNIZATION —*Indications* —Active immunization should be carried out in

a) Persons engaged in occupations in which the disease is likely to be encountered—farmers welders truckdrivers military personnel etc

b) Children whose activities more or less constantly expose them to the hazards of this disease In children tetanus prophylaxis is

usually combined with protection against diphtheria and sometimes also pertussis

c) Persons previously immunized who are exposed to injuries which might result in tetanus

d) Persons taking extensive trips in whom it may be desirable to administer a combination of tetanus toxoid and typhoid antigen

Materials—Two types of toxoid are used in active prophylaxis[4] Fluid Tetanus Toxoid is supplied in packages of three vials containing 1 cc each and in vials of 30 cc. by the following

Lederle Laboratories Inc. (also one supplementary dose vial of 1 cc.)
Eli Lilly and Co
Sharp & Dohme Inc.
Wyeth Inc.

Tetanus Toxoid Alum Precipitated, is available in 0 5 cc. and 1 cc. vials sufficient for one immunization, and in 5 cc and 10 cc. vials for five immunizations from the following

Lederle Laboratories Inc
Eli Lilly and Co
National Drug Co
Parke Davis & Co
Pitman Moore Co
Sharp & Dohme Inc
E R. Squibb & Sons
Wyeth, Inc

For immunizing against both diseases Tetanus Toxoid Typho-Bacterin is supplied in vials for one and for eight immunizations by

Sharp & Dohme Inc.

Typhoid Paratyphoid Vaccine Tetanus Toxoid is supplied in three 1 cc. vials and one 10 cc. vial by

Parke Davis & Co

Methods—Alum precipitated toxoid is definitely superior but because of a few reported accidents in adults some prefer fluid toxoid in immunizing *adults*

[4]The following new preparat ons are replacing the respective Lederle products See footnote 2 page 113
Tetanus Toxo d Flu d Purogenated 1 5 cc and 7 5 cc. vials for one and five immunizations
Tetanus Toxoid Refined Alum Precipitated Purogenated 1 cc. and 5 cc vials for one and five immunizations

The fluid toxoid is given at intervals of two to four weeks whereas the alum precipitated toxoid is administered at intervals of three to six weeks With both materials the first dose is 0 5 cc followed by a second and a third dose of 1 cc One year after the initial immunization and every year thereafter *a booster dose of 0 5 cc is given A booster dose is also given at the time of possible exposure to tetanus* If possible the booster dose at the time of injury should be *tetanus toxoid alone,* and not in combination with other antigens

Tetanus toxoid typho-bacterin and typhoid paratyphoid vaccine tetanus toxoid are administered *subcutaneously* in doses of 0 5 cc 1 cc and 1 cc at four week intervals Combined active immunization is now practiced against tetanus diphtheria and whooping cough (pp 116 and 188)

Contraindications—Few reactions have been encountered in children In adults and in older children local and general reactions occur more frequently

PASSIVE IMMUNIZATION—*Indications*—Passive immunization against tetanus should be carried out in any dirty and/or penetrating wound unless the patient has been actively immunized with tetanus toxoid in which event he should receive a booster injection of toxoid (see active immunization)

The question of protecting against gas gangrene should also be considered It must be emphasized that tetanus can develop in non penetrating wounds such as brush burns

Materials—Tetanus Antitoxin derived from immune horse serum is supplied in packages for prophylactic and therapeutic use by

Lederle Laboratories Inc prophylactic 1 500 units in syringes and 1 500 and 3 000 units in vials therapeutic, 20 000 and 40 000 units in vials

Eli Lilly and Co prophylactic vials of 1 500 units therapeutic, vials of 10 000 and 20 000 units

Parke Davis & Co prophylactic syringes or vials containing 1 500 and 5 000 units therapeutic syringes or vials containing 10 000 and 20 000 units

Pitman Moore Co vials or syringes containing 1 500 units

E R. Squibb & Sons prophylactic 1 500 units in vial or syringe and 3 000 unit syringes therapeutic 5 000 10 000 and 20 000 unit syringes

Wyeth Inc. Tubex package containing syringe and in vials

Tetanus Antitoxin, Bovine is supplied by

Sharp & Dohme Inc. 1 500 units per 'Vacule vial accompanied by 1 cc ampule vial of Normal Bovine Serum for sensitivity tests

Wyeth Inc 1 500 and 10 000 units in vials

Method—After testing for foreign serum sensitivity *1 500 units of tetanus antitoxin is given in a single subcutaneous injection (usually 1 cc)* In the presence of sensitivity to horse serum the bovine antitoxin should be given For prophylaxis against tetanus and gas gangrene the contents of a syringe or vial containing combined antitoxin (p 128) should be administered *subcutaneously*

Contraindications—Serum sickness shock and other constitutional reactions occur frequently enough to warrant great caution There must be strict adherence to the measures described for serum reactions (p 90) Fatal reactions have been reported in atopic persons

DIAGNOSIS

No immunologic method available

TREATMENT

Indications—The antitoxin must be given at the earliest possible moment after the diagnosis of tetanus has been made

Material—Tetanus Antitoxin (horse serum) is supplied by

Lederle Laboratories Inc vials of 20 000 and 40 000 units (despeciated)

Eli Lilly and Co vials of 10 000 and 20 000 units

Parke Davis & Co syringes and vials containing 10 000 and 20 000 units (despeciated)

Pitman Moore Co vials of 10 000 units (despeciated)

E R Squibb & Sons syringes of 5 000 10 000 and 20 000 units

Wyeth Inc vials and syringes

Method —Antitoxin is given *intravenously* or *intramuscularly* in a dose of 20 000 units or the dose may be divided and given both ways simultaneously Two or three more doses may be given *intramuscularly* within 24 hours and repeated as required The patient must be watched for constitutional reactions *Intrathecal* administration of antitoxin *is valueless* and *potentially dangerous*

Contraindications —These are the same as those listed for prophylactic administration of tetanus antitoxin

IMMUNITY

There is no natural immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Elimination of the disease depends on the success of antiaccident campaigns and on general immunization with tetanus toxoid

Trichinosis

INCUBATION PERIOD

None ascertained

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

SKIN TEST WITH TRICHINELLA EXTRACT —*Indications* —The skin test is of some diagnostic value when performed to substantiate a clinical diagnosis of trichinosis

Material —Trichinella Extract is available in a package containing two 1 cc vials one vial of Trichinella Extract in isotonic solution of sodium chloride and one control vial of isotonic solution of sodium chloride Merthiolate is added as a preservative It is prepared by

Lederle Laboratories Inc

Eli Lilly and Co

Method—A dose of 0 01 to 0 02 cc of the extract is injected *intracutaneously* on the outer aspect of the upper arm a like amount of control fluid is injected in the same manner in a corresponding area of the other arm Urticarial reactions are read immediately (10–20 minutes) and the tuberculin type reactions are read at 48 hours

A positive reaction to the extract (and negative to the control solution) is usually of the immediate urticarial type although rarely there may be a delayed 48 hour tuberculin type reaction

It should be remembered that a positive reaction means *only* that the *patient has had a Trichinella infestation A positive reaction* does not necessarily mean that the presenting symptoms are caused by the presence of the organism or indeed, that the organism is present at the time of the test A negative reaction does not rule out the possibility of Trichinella infestation the patient may not be allergic to the extract in the presence of active infestation or in acute trichinosis may not yet have developed skin sensitivity which usually appears in about 14 days

Antibodies in the blood serum can be demonstrated by precipitin or complement fixation tests which offer a useful adjunct to the skin test However such serologic tests for antibodies are not office procedures

Contraindications—Ill effects from the application of this test are not known In case of untoward reaction administration of epinephrine should be tried

TREATMENT

No immunologic method available

IMMUNITY

If the infestation does not terminate in death its progress is eventually checked by encapsulation of the trichinellae by the body in which true immunologic reactions probably play a considerable role There is no information on the extent of clinical immunity against a second infection

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

The infection is usually acquired by eating raw or insufficiently cooked pork. Thus infestation could be eradicated by proper public health measures in particular by stopping the feeding of raw garbage to pigs and by a proper system of meat inspection This desirable goal—the eradication of trichinosis—has indeed been reached in some countries However statistics from autopsies show that a surprising percentage of the population of the United States has at some time or other been infected. Under these circumstances pork that does not carry the official stamp of the U S Public Health Service must be considered potentially dangerous and should be eaten only if *thoroughly* cooked

Although the overwhelming majority of infections are contracted from pork many other animals are susceptible and, in rare cases may also infect man if their meat is consumed without proper and thorough cooking

Tuberculosis

This discussion pertains chiefly to visceral tuberculosis and particularly to tuberculosis of the lungs and meninges A detailed discussion of the tuberculoderms is presented in Chapter 6

INCUBATION PERIOD

For the first infection in childhood probably two to four weeks

PRODROMAL SYMPTOMS

Vague and not specific See indications for skin test with tuberculin

PROPHYLAXIS

ACTIVE IMMUNIZATION —*Indications* —Vaccination with BCG (Bacillus Calmette Guerin) is a specific method of immunizing against tuberculosis but is not generally used in this country

Material —In the United States the BCG vaccine is available only to public health groups not to individuals Requests should be addressed to Tice Laboratories and Clinics Cook County Hospital, Chicago 12 Instructions issued with the material should be closely followed

DIAGNOSIS

Skin Test with Tuberculin —Tuberculin by intracutaneous injection or by topical application (patch test) will produce a specific reaction in most persons who have had an infection with Mycobacterium tuberculosis *In children up to 2 the tuberculin skin test is generally accepted as of value in determining the presence or absence of active tuberculous infection* In this age group a positive test means probable active infection

As the child grows older the chances of past infection and quiescent lesions grow greater and the positive reaction is more likely to indicate a past rather than an active infection *With the decreasing existence of tuberculous infection throughout the community the diagnostic importance of the test is increasing* even in older children and in adults

Indications

a) In infants the tuberculin test is indicated in the presence of prolonged fever in chronic pulmonary infiltration chronic enlargement of the mediastinal glands or chronic bone infection and in the presence of a large spleen or unsatisfactory weight curve In older people it is indicated in a patient who has frequent colds especially if associated with a brassy cough in one who tires easily displays anorexia loss of weight transient periods of mild fever or night sweats and in one who has physical or x ray evidence of pulmonary infiltration

b) As a public health measure the test is of particular value in screening out infected persons from normal ones

c) The test is often done routinely at 5–6 years

d) The test is done when the child is discovered to have been in contact with a case of open tuberculosis

e) Other uses of the tuberculin test are discussed under tuberculoderms

Materials —Old Tuberculin Koch (OTK) Concentrated old tuberculin in a vial or syringe together with vials of diluent convenient for making up the usual dilutions for testing, is supplied by many city and state departments of health and by the following

Cutter Laboratories
Lederle Laboratories Inc.
Eli Lilly and Co
National Drug Co
Wyeth Inc.

Ready made single dilutions and suitable serial dilutions are supplied by

Cutter Laboratories
National Drug Co

Some of these concerns also put up old tuberculin in capillary tubes for single (scratch) tests

Purified Protein Derivative (PPD) This is a purified dry derivative of tuberculin. Tablets in first strength (0 00002 mg per test) and second strength (0 005 mg per test) are supplied in vacule and ampule vials Diluent is added to the vial to give a first strength or a second strength solution

Parke Davis & Co packaged for 1 10 20 100 and 500 tests with each strength.

Sharp & Dohme Inc packaged for 1 10 100 and 250 tests with each strength (Lyovac)

(Each package has an ampule containing the required amount of diluting fluid in addition to the ampule containing the required amount of PPD in tablet form.)

Tuberculin Patch Test. Under the name Tuberculin Patch Test (Vollmer) a cellophane wrapped assembled adhesive strip having two test squares saturated with tuberculin and one control square of filter paper saturated with concentrated *uninoculated* broth is marketed by

Lederle Laboratories Inc

Methods—Intracutaneous Test The most generally accepted technic is the intracutaneous or Mantoux test with OTK or PPD Using old tuberculin 0 1 cc of 1 10 000 dilution (0 01 mg) is injected intracutaneously The reaction is read in 48–72 hours (See 24–48 hour tuberculin type reaction on page 45) An area of erythema with or without induration indicates a positive test If negative the test may be repeated with a 1 1 000 dilution (0 1 mg) If the second test is negative the patient is usually considered to be free of tuberculous infection As a rule a control test should be performed using the diluent (normal saline solution) or *preferably the blank, uninoculated sterile broth*

The test may also be done with the two dilutions of purified protein derivative of tuberculin. PPD although a purer product has few if any special advantages Solutions of PPD are not stable for more than two days whereas the higher concentrations of old tuberculin may if properly stored remain potent for six months PPD comes in two dilutions A patient should be negative to the second strength before being considered free of infection

Patch Test with OTK. *In individual cases when it is imperative to avoid injections, or in working with great numbers of children the patch test technic is of value* The patch test corresponds to the first strength of PPD or the 1 10 000 dilution of OTK

Some authorities contend that in tuberculosis in childhood the patch test will give as great an incidence of positive tests as that elicited by the intracutaneous or Mantoux test All agree that after 15 years of age an increasing number of persons with positive reactions to intracutaneous tests are negative to patch tests These facts conform to the rule that children s skin is usually more permeable than the skin of adults

Other advantages of the patch test are (1) it can be done by an assistant with little training and (2) no sterilization facilities are needed.

The skin over the sternum or the upper back lateral to the spine or on the inner aspect of the forearm is cleansed with acetone and the patch test is applied with pressure from the warm palm of the hand The patch is *removed in 48 hours* and *read at 72 or 96 hours* A group of tiny vesiculopapules on a reddened indurated area usually of a cleancut square shape is a positive reaction

As stated in children there is a high degree of correlation between positive and negative patch tests and intracutaneous reactions However a negative patch test in a suspicious case should be checked by the Mantoux test

Under certain conditions a *negative tuberculin test* may be misleading Overwhelming miliary tuberculosis measles influenza whooping cough typhoid scarlet fever poliomyelitis diphtheria

and other disease conditions (p 376) may cause a patient with a tuberculous infection to have a negative test A true positive test checked by proper controls always indicates an infection, this how ever *may be inactive* No studies are yet available to prove a relationship between the size or type of the skin reaction and the size or type of the visceral lesion

The younger the child with a positive test the *more recent the infection* and for this reason alone the more probable the presence of some activity Every positive test in a child should therefore be followed by clinical and x ray studies

When tuberculous *infiltrative lesions* appear in a child known to *have been negative* to recent (routine) tuberculin testing the *prognosis is relatively good* and the treatment need be only bed rest and removal from the contact However if a *routine* tuberculin test has *recently been positive* the pulmonary *infiltration* is likely to be a reinfection or a lighting up of a phthisis type of disease and *prolonged rest or collapse therapy* may be the required treatment.

Recently there has been some doubt cast on the efficiency of tuberculin testing to screen out cases of tuberculosis occurring in large groups of subjects In a sizeable proportion of children the x ray seems to establish the diagnosis *before* the tuberculin test becomes positive In addition in large scale case finding projects inconsistency has been encountered between general incidence of tuberculosis and incidence of positive tests among various population groups X ray visualization on paper film or on miniature negative film was used extensively by the Armed Services and is becoming the method of choice in many large screening trials Nonpulmonary infections relatively rare in the United States are of course not discovered by pulmonary radiography

Contraindications —Use of the tuberculin test is contraindicated in a patient in whom an active pulmonary lesion is suspected In such a case x ray rather than tuberculin testing should be used to confirm the diagnosis Even in a child with an inactive lesion the test should not be repeated too often Such a child is frequently seen by many

doctors and in many clinics and a new set of tests will often be done without reference to previous recent injections of tuberculin The important untoward reactions to tuberculin follow

Constitutional Reactions These are more common in children over 4 and in adults and with the use of the higher concentrations They are not usually of the explosive type such as those following foreign serums and atopic allergens but are usually delayed febrile and general grip like reactions

Focal Reactions These may be in the pleura meninges lymphatic nodes eyes skin or at any other focus

Local Reactions at Site of Injection Local reactions may be severe to the point of vesiculation and necrosis This is more likely in children of school age and in adults and after the use of the higher concentrations Local reactions usually subside within a few days

Complications are of course less apt to occur when the patch test is used. With the Mantoux test the incidence of untoward reactions rises sharply when 0 1 mg OT is used first tests should therefore always be done with 0 01 mg or less

TREATMENT

Treatment of a tuberculous infection by administration of tuberculin is carried out rarely and only by a very few specialists

IMMUNITY

A great difference in individual susceptibility is the rule but there is no complete natural or acquired immunity The course and reaction of tuberculous infection is however greatly modified by various factors one in particular is the immunologic changes resulting from the first infection (see tuberculoderms)

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

For the present the practicable methods of prophylaxis *consist principally in endeavors to reduce the exposures to virulent bacilli through hygienic and public health measures* These endeavors are guided by the recognition of the following facts

1 Repeated exposures to relatively large quantities of virulent bacilli constitute the most powerful factors leading to progressive disease The most common forms of exposure are direct respiratory contact and ingestion of milk from infected udders

2 Both the inherited constitution and the acquired state of health exert strong influences on the degree of individual susceptibility

3 Infancy is the age in which exposure to infection is most inclined to produce dangerous and progressive disease

4 Other particularly hazardous age periods may perhaps occur at puberty in the early twenties and during senescence

5 A lessened resistance is likely during active or convalescent stages of certain other diseases (measles whooping cough etc)

Taking these facts into account modern public prophylaxis of tuberculosis relies mainly on improved living conditions housing and other sanitary measures for the general reduction of exposures—including of course the isolation of persons who are disseminators of large numbers of virulent bacilli and the pasteurization of all milk. The finding of cases is helped by large scale studies employing tuberculin testing and pulmonary x ray films together with clinical and bacteriologic examinations To these measures are added the best available methods for protecting from exposure all infants as well as all individuals during the other aforementioned recognized periods of greatest susceptibility Moreover the general and individual susceptibility to infection superinfection and reinfection is reduced by all measures known or reputed to increase general resistance to tuberculous disease

From recent work it appears that a surprising percentage of the population in this country gives positive skin tests to histoplasmin, an extract prepared from Histoplasma capsulatum Although this fungus formerly was thought to be only a rare infective agent for man it is concluded that subclinical infections with Histoplasma occur frequently The correlation of skin reactivity to histoplasmin found in these tests with pulmonary calcification found in roentgen examinations of the lungs makes it probable that calcified hilus

glands are frequent sequelae of an infection with Histoplasma This is of practical importance because it tends to explain discrepancies between x ray findings and tuberculin reactions

Tularemia (Rabbit Fever, Deer Fly Fever)

INCUBATION PERIOD

Three to five days May vary up to 21 days

PRODROMAL SYMPTOMS

Sudden onset with chills fever aches and vomiting

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

A skin test with Pasteurella tularensis vaccine for the 24–48 hour or tuberculin type reaction has been described as diagnostic be fore the agglutination test becomes positive Materials are not com mercially available The agglutination test though reliable is not an office procedure

TREATMENT

Streptomycin promises to be of great value in the treatment of tularemia Antitularemic horse serum is probably of some value in many cases

Material—Antitularemic Serum (horse) is supplied in a package containing one vacule representing 30 cc of original serum, one vial (15 cc) of pyrogen free sterile distilled water for restoring serum to one half its full volume and for test and hyposensitizing material, one 1 cc vial of normal horse serum (diluted 1 10) and is manufacrured by

Sharp & Dohme Inc (Lyovac)

Method—In mild cases 7 5 cc of restored double concentrated serum is injected *intravenously* twice daily on successive days Cases of septicemic or typhoid type require much larger amounts and in such cases up to 75 cc of this serum can be given intravenously twice daily

Contraindications—Serum sickness shock and other constitutional reactions warrant great caution and necessitate strict adherence to preventive measures

IMMUNITY

One attack confers immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

The disease is transmitted chiefly through the handling of wild rabbits It may also be contracted from bites of ticks and flies Finally cases have followed ingestion of insufficiently cooked rabbit meat It is not spread from human to human

It is suggested that blood samples from suspected cases be sent to the National Institute of Health Washington D C for culture and agglutination

Typhoid Fever and Paratyphoid Fever

As generally diagnosed typhoid fever is a clinical rather than a bacteriologic entity The picture of typhoid fever may be caused not only by the typhoid bacillus but by various members of the paratyphoid group particularly those of groups A B and C_1 The percentage of fatalities in infections caused by the by no means rare Salmonella group C_1 is higher than that caused by the typhoid bacillus but there is no vaccine available in this country which provides protection against micro-organisms of the group C_1

INCUBATION PERIOD

Seven to 20 days

PRODROMAL SYMPTOMS

Fever malaise gastrointestinal symptoms

PROPHYLAXIS

ACTIVE IMMUNIZATION —*Indications*

a) Immediately in every person who has had contact with a case of typhoid fever or with a carrier of Eberthella typhosa

b) In persons living where typhoid is endemic a booster shot every second spring

c) In persons expecting to enter areas where typhoid fever is endemic Military personnel or children going to a camp or rural area might well receive the combined typhoid tetanus toxoid injections

Materials—Bacterial vaccines are generally considered to be of value in the *prophylaxis* but *not* in the *treatment* of typhoid fever Many reputable firms supply typhoid vaccine made from E typhosa alone or a *triple combined vaccine* which also protects against paratyphoid A and B

Typhoid Vaccine which usually comes in packages of three vials each containing one dose contains from 500 to 1 000 million micro organisms per cc. and is supplied by

Cutter Laboratories	E R Squibb & Sons
Eli Lilly and Co	U S Standard Products Co
National Drug Co	Wyeth Inc.
Parke Davis & Co	

Typhoid Paratyphoid (triple) Vaccine contains 1 000 million typhoid bacilli and 500–750 million each of paratyphoid bacilli A and B per cc and is supplied in the following packages

Abbott Laboratories three 1 cc ampules ten 3 cc vials 6 cc. and 20 cc vials

Cutter Laboratories three 1 cc. vials 20 cc vial for eight immunizations.

Lederle Laboratories Inc three 1 cc vials 5 cc and 20 cc vials

Eli Lilly and Co three 1 cc vials 5 cc. and 20 cc. vials.

National Drug Co three 1 cc vials 5 cc 20 cc and 30 cc. vials

Parke Davis & Co three 1 cc. vials ten 2 5 cc vials 20 cc. vials

Sharp & Dohme Inc three 1 cc. vials 5 cc and 20 cc. vials 30 vial packages for 10 complete immunizations

E R. Squibb & Sons three 1 cc. vials 5 cc and 20 cc vials box of 10 immunizing treatments

The Upjohn Co 20 cc vials

U S Standard Products Co three 1 cc. vials 5 cc 10 cc. and 20 cc vials

Wyeth Inc three 1 cc vials 5 cc 10 cc and 20 cc. vials

Combined Typhoid Paratyphoid Vaccine Tetanus Toxoid (alum precipitated) is supplied in three 1 cc vials and in one 10 cc. vial by

Parke Davis & Co

Tetanus Toxoid Typho-Bacterin in vials for one and eight immunizations is supplied by

Sharp & Dohme Inc.

Oral typhoid vaccine while listed here is of doubtful value and should be used only if subcutaneous or intradermal routes cannot be used. It is supplied by

Eli Lilly and Co 'Typhoral' in bottles of 3 pulvules for one complete immunization and 100 pulvules for 50 immunizations

Oral Typhoid Mixed Vaccine containing in addition the two paratyphoid micro organisms is put up in bottles for 1 10 and 50 immunizations by

Eli Lilly and Co

Capsules of typhoid vaccine in bottles of 10 each (one immunization) are supplied by

The Wm. S Merrell Co Oravax

Methods—*Typhoid vaccine* is given *subcutaneously* When the vaccine is obtained in immunizing sets of three vials each the first vial has half the dose of the other two and is usually so marked Give the three vials in succession two weeks apart When using the bulk packages the doses are 0 5 cc 1 cc and 1 cc at the same intervals Younger children do not tolerate the vaccinations well and it may be advisable to divide the first two doses into two injections each For children under 4 if immunization is necessary the dosage should be 0 05 cc 0 1 cc and 0 1 cc

Immunity lasts about two years To be safe a booster injection of 0 5 cc. *subcutaneously* should be given *every other spring* Some favor a booster dose of 0 1 cc using the *intracutaneous* route but the

original injections are usually subcutaneous and in the doses de scribed

Combined typhoid tetanus antigen is given to persons going to areas where they may be exposed to both diseases Administer *sub cutaneously* 0 5 cc 1 cc and 1 cc at intervals of three to four weeks

Oral typhoid vaccination has limited indications especially since with reasonable care untoward effects from subcutaneous injections should be minimal The main use of oral vaccination would seem to be in catastrophic circumstances when certainty of protection is sacri ficed for an attempt at *mass immunization* Administration is simple One pulvule of the typhoid vaccine is taken one half to one hour before breakfast on three successive mornings With Merrell Oravax capsules doses of 2 capsules for adults and 1 for children are given on the first second third sixth and ninth days

Contraindications —There may be mild reactions of local redness swelling and pain some malaise and moderate fever following the injection The systemic reactions are usually controlled with aspirin Vaccine should not be given in the presence of fever Reactions to the oral vaccines are rare but may consist of mild to moderate gastrointestinal disturbances

PASSIVE IMMUNIZATION —None

DIAGNOSIS

No immunologic method available for office use

TREATMENT

No generally accepted immunologic method available

IMMUNITY

One attack of the disease usually confers permanent immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Constant care of water and food supply is indicated. Isolation of carriers and of patients sick with the infection is important as is mass immunization of individuals in endemic areas

Typhus Fever (Epidemic Type)

INCUBATION PERIOD

Six to 14 days

PROPHYLAXIS

Of great value

ACTIVE IMMUNIZATION —*Indications*—Immunize persons living or traveling in areas in which epidemic typhus fever exists and laboratory personnel exposed to the virus The United States Navy considers that residence or travel in the following areas necessitates active immunization Mexico Guatemala British Honduras Venezuela Colombia Ecuador Peru Asia, Africa and Europe except Scotland, England and Sweden

Material—Typhus Vaccine prepared from yolk sac infected with *murine* typhus Rickettsia, and formalin treated is distributed in packages of three 1 cc vials for one immunization and in 20 cc vials for immunizing large groups by

Lederle Laboratories Inc
Eli Lilly and Co
Parke Davis & Co

Method—Two doses of *1 cc* each are given *subcutaneously* one week apart The duration of immunity is as yet undetermined A booster dose of 1 cc is given every four to six months if the possibility of exposure continues to exist In immunized persons the disease is greatly modified if it does occur and no deaths have been recorded.

Contraindications—The vaccine prepared from the yolk sacs of chick embryos has caused undesirable local or generalized reactions occasionally (but fortunately rarely) in persons allergic to egg chicken or chicken feathers Immunization of such persons should not be attempted in case of necessity the dose should be further subdivided and administered under close supervision.

PASSIVE IMMUNIZATION—No method of recognized value is available

TREATMENT

The antiserum must be given early *preferably in the prodromal stage* of the disease The serum however seems at present unobtainable It used to be administered in four doses of 20 cc each *subcutaneously*

IMMUNITY

Typhus leaves a long lasting and possibly permanent immunity Cases of second infections are known however

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Typhus is louse borne and therefore public health measures center around the elimination of the louse through cleanliness and decontamination For the latter purpose DDT has extraordinary usefulness

Whooping Cough (Pertussis)

INCUBATION PERIOD

Five to 10 days

PRODROMAL SYMPTOMS

Rhinitis sneezing lacrimation and a cough which may persist for two weeks before typical paroxysms appear

PROPHYLAXIS

The pertussis bacillus contains two antigens (1) agglutinogen against which immune antibody is found in human serum and (2) toxic antigen (toxin) the clinical significance of which is still in doubt

ACTIVE IMMUNIZATION—*Indications*

a) Routinely in every child at about 5 months of age

b) In children up to 5 years who have not had previous inoculation or the disease itself

c) A booster injection is indicated whenever a child previously immunized is exposed to a case or is admitted to school or to another institution

d) Undenatured bacterial antigen (Krueger) or pertussis antigen (detoxified) is sometimes recommended for immunization during an epidemic or after exposure

Materials—H Pertussis Vaccine (Phase I) is the antigen usually tested in clinical studies and most generally accepted as valuable in active immunization.

> The exact Sauer formula of Hemophilus pertussis vaccine using human blood in the media for growth, is manufactured only by Parke Davis & Co It is made in one strength 15 000 million micro-organisms per cc and is bottled in 6 cc vials for one complete immunization and in 24 cc vials for four complete immunizations

Other manufacturers now follow the general technic of Sauer but use other than human blood The vaccine is made in two strengths 10 000 million and 20 000 million micro organisms per cc More recently the double strength vaccine (20 000 million micro-organisms) has been abandoned by some manufacturers owing to severity of reactions. Most of the houses listed make a vaccine containing 15 000 million micro organisms per cc The following firms package the single strength in vials for one and four immunizations

Lederle Laboratories Inc	U S Standard Products Co
Eli Lilly and Co	The Upjohn Co
National Drug Co	Wyeth Inc.
E R Squibb & Sons	

The double strength alone is supplied in packages for one and four immunizations by

Kirk Laboratories
Lederle Laboratories Inc.
Sharp & Dohme Inc.

> Cutter Laboratories supply a superconcentrate in vials of 2 5 cc (one immunization) 10 cc and 25 cc containing 40 000 million micro-organisms per cc They also furnish the

regular double strength vaccine in vials double the size for the same number of immunizations

U S Standard Products Co supply a vaccine containing 40 000 and 60 000 million micro-organisms per cc. in vials for one and five immunizations

Pertussis Vaccine Alum Precipitated is a regular vaccine phase I precipitated with alum to gain the advantages inherent in alum precipitated antigen.

Eli Lilly and Co vials containing 40 000 million micro-organisms per cc. for one and five immunizations

Parke Davis & Co vials containing 15 000 million micro-organisms per cc. for one and four immunizations

The Upjohn Co 3 cc and 10 cc vials containing 10 000 million micro-organisms per cc.

Pertussis Vaccine Diphtheria Toxoid Alum Precipitated Combined, contains 40 000 million pertussis micro-organisms per cc. plus the usual amount of diphtheria antigen contained in this amount of injectable material. This vaccine toxoid combination is packaged by

Eli Lilly and Co for one and five immunizations
National Drug Co for one and five immunizations
Parke Davis & Co for one and four immunizations
Sharp & Dohme Inc for one and three immunizations
E R. Squibb & Sons for two immunizations
The Upjohn Co vials of 3 cc. and 10 cc.

Diphtheria Tetanus Pertussis Combined Alum Precipitated is a vaccine toxoid. Each cubic centimeter contains one immunizing dose each of diphtheria and tetanus toxoid alum precipitated plus pertussis bacterin.

Cutter Laboratories for one and five immunizations
Eli Lilly and Co for one and five immunizations
National Drug Co for one and five immunizations
Sharp & Dohme Inc for one and three immunizations

Undenatured Bacterial Antigen (Krueger) is manufactured from bacterial filtrates by Lilly and is packaged in 5 cc. and 20 cc vials It is made from H. pertussis cultures or in combined form from pertussis and other micro-organisms found in the upper respiratory tract

Pertussis Antigen (Detoxified) is manufactured by Lederle by a special process of bacterial autolysis Vials of 20 cc. each and packages of three 2 cc vials are available

Pertussis Immunogen Pertussis Serobacterin Endotoxin Intranasal Antigen and Dextrified Antigen have not been found to have special advantages over those listed Vaccines combining H pertussis with other bacteria found in the respiratory tract are generally of little additional value

Methods —All vaccines are injected *subcutaneously*

H Pertussis Vaccine (Phase I) The advantage of the Sauer vaccine over other phase I vaccines is that the medium for the former contains human rather than foreign blood This diminishes the possibility of sensitization to animal serums although many workers discount this possibility

Directions for use of H pertussis vaccine prepared on mediums not containing human blood vary slightly for products of different manufacturers Packaging is therefore given in terms of number of immunizations rather than number of cubic centimeters In general the following dosage is given for single strength vaccine (10 000 million micro organisms per cc) injections of 1 cc 1 5 cc 1 5 cc and 3 cc at weekly intervals (the fourth dose is divided in two and 1 5 cc is injected into each arm) Total injected is 7 cc or 70 000 million micro organisms

When using double strength vaccine (20 000 million) give three single injections (1 cc 2 cc and 2 cc) at intervals of two weeks a total of 100 billion micro-organisms In older children give a total of 6 cc

Vaccine containing 15 000 million micro-organisms per cc is given in doses of 1 cc 2 cc and 3 cc at monthly intervals The last dose may be split into two injections of 1 5 cc and one given in each arm Total dosage is 90 000 million micro-organisms

The Cutter Laboratories superconcentrate (40 000 million micro-organisms) is given in doses of 0 5 cc, 1 cc. and 1–1 5 cc at monthly intervals

Injections of any pertussis vaccine should be made *subcutaneously* and in the case of nonprecipitated vaccines as superficially as possible Use only a heat sterilized cooled syringe The vaccine should not be given immediately after it is removed from the re frigerator but should be permitted to remain at room temperature for a few minutes Shake well If a mucoid precipitate persists after shaking the vaccine should not be used

Whereas opinion favoring the use of pertussis vaccine is not unanimous the *great weight of evidence favors its routine use It prevents whooping cough in a high proportion of exposed children and when it does not prevent the disease often minimizes the intensity* Some degree of immunity is developed by the end of the first month, but the height of protection is not attained before the fourth month Immunity seems to last about four to six years However during that time exposure to whooping cough and subclinical infec tions which do not become manifest owing to the vaccine-conferred immunity often give the child an opportunity to develop greater natural immunity Nevertheless a booster injection of 2 cc of vac cine (15 000 million organisms per cc) is indicated when the child is known to have been exposed to whooping cough and also when he enters school

Pertussis Vaccine Alum Precipitated This is administered at in tervals of two weeks in doses of 0.2 cc 0 3 cc and finally 0 5 cc Subcutaneous injection is somewhat deeper with precipitated vac cine Care should be taken not to repeat injections in the same spot The Parke Davis alum precipitated vaccine is given in three doses of 0 5 cc each at intervals of one month

It is thought that precipitation with alum makes possible the slower absorption of the vaccine and, hence a higher efficiency The use of smaller individual doses and the smaller total dosage of micro-organisms are other advantages This material is generally considered of value in prophylaxis

Pertussis Vaccine Diphtheria Toxoid, Alum Precipitated. This ma terial is said to be of value in immunizing simultaneously against

both diseases It also has the advantages of alum precipitation The Squibb preparation is given in four doses of 1 cc each at four week intervals The National Drug preparation is given in three doses of 1 cc each the first two one week apart the third injection one month after the second The Lilly preparation is given in three doses of 0 2 cc 0 3 cc and 0 5 cc at monthly intervals The Parke Davis preparation is given in three injections of 1 cc 2 cc and 3 cc at monthly intervals

Diphtheria Tetanus Pertussis Combined This is said to be of some value in immunizing against all three diseases simultaneously It is given in three doses of 1 cc each at intervals of one month The Cutter material (alhydrox) is given in doses of 0 5 cc 0 5 cc and 1 cc

(There is no contraindication to using the three individual older preparations in combined immunization against these three diseases At a single visit the patient can be given three injections each from a separate syringe or one injection using pertussis vaccine fluid diphtheria toxoid and alum precipitated tetanus toxoid in the same syringe)

Undenatured bacterial antigen (Krueger) is not used in routine active immunization It is used only when *rapidity* is essential e g after exposure to the disease or during an epidemic We know of no advantage in using this combined antigen Administer *subcutaneously* An initial dose of 1 cc is followed with 2 cc doses daily for a total of five injections The pertussis antigen (detoxified) is given *subcutaneously* in three injections of 2 cc each at weekly intervals

Injections of vaccine and of the other antigenic substances are generally of no prophylactic value during the incubation period or prodromal period of whooping cough

Contraindications—Reaction to many of the whooping cough antigens is common at all ages and very common in older children and adults The reaction usually consists of local redness swelling and pain Less often a moderate rise in temperature occasionally to 103 F also occurs particularly after the second injection In such

patients the immunization should not be discontinued but the full remaining dose should be *divided over a longer than usual time*

Reactions are similar to those seen after injections of other bacterial vaccines Preparations containing alum should not be given to children of school age or over No treatment is necessary for the nodule which sometimes persists at the site of injection in fact its appearance is considered beneficial by some Occasionally a sterile or infected abscess appears

The incidence of reactions and complications is reduced if the instructions are followed carefully When fever appears prescribe aspirin Do not apply wet dressings or heat to the local reactions

PASSIVE IMMUNIZATION —*Indications*

a) To provide rapid though temporary immunity in exposed persons particularly in children under 3

b) To provide rapid though temporary immunity in exposed children particularly those under 1 in whom a previous active immunization may not have had time to become effective

Materials—Human Pertussis Convalescent Serum and Human Pertussis Hyperimmune Serum may be obtained from the convalescent serum centers

Pertussis Immune Rabbit Serum is prepared by

E R Squibb & Sons 1 cc vials each containing 15 000 units

Ayerst, McKenna & Harrison Ltd 10 cc vials each containing 10 000 units of antiendotoxin.

Methods—Give 20 cc human convalescent serum or human hyperimmune serum *intramuscularly* as soon as possible after exposure These serums are said to be of value in producing an immediate immunity which lasts for about two weeks The immune rabbit serum is said to be of some value in conferring passive immunity Give the contents of one vial *intramuscularly*

Contraindications—The usual precautions—history of *atopy* ophthalmic or intradermal tests—against reactions due to foreign

serum sensitivity must be taken in using rabbit serum Human serum rarely gives untoward reactions

DIAGNOSIS

No skin test or other immunologic test is *generally* accepted as of value in the *diagnosis* of pertussis or in ascertaining the presence or absence of *immunity* to pertussis There is however a Pertussis Agglutination Test Outfit supplied by Eli Lilly and Company The package contains five capillary tubes of colored pertussis antigen and comparator cards which are used to determine whether a subject has circulating immune antibody The relationship of this finding to clinical immunity has not been established

TREATMENT

Indications—In addition to general therapeutic measures for combating the fatigue cough vomiting and anorexia of whooping cough *immunologic methods should be tried in severe cases*, particularly in those occurring in the very young among whom the mortality rate is still high

Materials—Human Pertussis Convalescent Serum and Human Pertussis Hyperimmune Serum obtainable from serum centers are said to be of value in the *treatment* of some cases Immune rabbit serums prepared by the manufacturers listed on page 189 are said to be of some value Undenatured Bacterial Antigen is of value in some cases (sources on p 185) Pertussis Antigen, Detoxified, is also of value in some cases (sources on p 186)

Methods—The human serums are given in doses of 20 cc *intramuscularly* and repeated every one to three days as needed The rabbit immune serum is also given *intramuscularly* In treatment give at least two vials (30 000 units) at a single dose

Undenatured bacterial antigen is given *subcutaneously* Start with doses of 0 5 cc. and increase to 2 cc or more daily injections are given for a total of 10–15 doses It is advised that a fraction of each dose be given *intracutaneously* Pertussis antigen (detoxified) is given *subcutaneously* in doses of 2 cc. at two day intervals for three

weeks Pertussis vaccine (combined) is given in the same dosage that for prophylaxis but at weekly intervals

Contraindications—Before administering rabbit serum the usu precautions against foreign serum hypersensitivity must be take Reactions from the use of human serum while not unknown a rare Reactions to undenatured bacterial antigen are negligible

IMMUNITY

Permanent immunity is acquired from an attack of the disea After vaccination there is a high rate of immunity and this prote tion usually *lasts for about four to six years* It should be noted th immunity to H pertussis does not mean immunity to H parape tussis an organism which may also cause the clinical symptoms whooping cough

Otherwise there is practically universal susceptibility to the d ease There is no evidence of immunity after subclinical infectio unless the child has been previously immunized Adults are frequen ly susceptible—whooping cough is that childhood disease whi a parent is most likely to contract from the child

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

The best public health measure thus far available is universal im munization Quarantine is impracticable in a disease in which the is such a prolonged period of contagion and in which diagnosis so difficult in the first two weeks

Each case is produced by contagion from another active ca there are no pertussis carriers The disease is transmitted by dire respiratory contact Food and milk play no role in transmissio

Yellow Fever

INCUBATION PERIOD

Three to five days

PROPHYLAXIS

ACTIVE IMMUNIZATION—*Indications*—Active immunizati with attenuated virus is generally considered to be of value for p

sons living or traveling in areas where yellow fever is prevalent and for laboratory personnel working with the virus

Material—For technical reasons it has been found advisable to distribute the material for active immunization (an attenuated strain of the living virus) only through U S Public Health Clinics

Method—The contents of a vial containing the virus are injected *subcutaneously* A booster dose is given every two years if the possibility of exposure continues to exist

Contraindications—The incidence of serum jaundice has been reduced to practically zero by discontinuing the use of human serum for diluting the vaccine (It is today considered likely that the jaundice experienced in the early days of the war was a form of infectious hepatitis transmitted by the human serum) The vaccine should not be given concomitantly with cowpox virus or to persons suffering from any known virus disease

DIAGNOSIS

No immunologic method available

TREATMENT

Immune serum has been used with some benefit both during the incubation period and after the onset of symptoms Unfortunately however the serum is not generally available

IMMUNITY

One attack does not always confer immunity

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Elimination of the disease depends on elimination of the Stegomyia calopus mosquito and prevention of mosquito bites

Chapter Four

IMMUNOLOGIC PRINCIPLES OF TRANSFUSION REACTIONS—THE Rh FACTOR

Alfred J Weil and Abram Kanof

Blood Typing

THE DISCOVERY of inheritable individual differences in the antigenic constitution of erythrocytes has turned out to be one of the major contributions of immunology to modern medicine The antigens in question are all located within the membranes that form the walls of the erythrocytes These membranes must have a rather complicated make up for we now recognize a considerable number of antigens some of which are and some of which are not found elsewhere in the body It is impossible to discuss the theoretical and clinical aspects of blood types in this book A comprehensive presentation of the whole matter may be found in *Blood Groups and Transfusion* by A S Wiener (Springfield Ill Charles C Thomas Publisher 1943)

This much can be said here by way of recapitulation There are four main blood groups which are characterized by the presence of antigens A and/or B namely A B AB and O (the letter O symbolizes the absence of both antigens) The counterpart of these antigens is found in agglutinating antibodies in the serum which are usually designated by the Greek letters α and β Thus blood group

A has antibody β in its serum group B has antibody α group AB has *neither and group O has both antibodies α and β*

It is important to be aware that there are no natural antibodies to the remaining antigenic components of the erythrocytic membrane.

The determination of blood groups for compatibility of type before transfusion is beyond the facilities of the practicing physician and should be done in laboratories equipped for this purpose However under the stimulus of the need of our Armed Forces for mass determinations of blood types methods have been developed which enable the practicing physician to make determinations of the most important antigenic properties with a great deal of reliability if the proper technic is used—a technic which is simple and needs no complicated apparatus This test should be used by the practitioner only as a preliminary test to be checked in a competent laboratory before transfusion is given or in situations in which no competent laboratory is available Serum in handy form for use by the general practitioner is now available from

Gradwohl Laboratories (St Louis) anti A and anti B human serums in 2 cc. bottles

Lederle Laboratories Inc human blood anti A and anti B groups in packages of 10 capillary tubes also in packages of 2 capillary tubes of each serum

In addition to the A and B antigens blood cells do contain a variety of inheritable antigens for which however no antibody is normally present in human serum The more important of these are designated M and N and Rh The last is of particular interest because of its relation not only to blood transfusion accidents but especially to the pathogenesis of erythroblastosis fetalis

Erythroblastosis Fetalis (Hemolytic Disease of Newborn)

It is now generally accepted that this disease is caused by the sensitization of the mother to a hereditary dominant blood factor

in the fetus Although on rare occasions the responsible fetal anti gen may be a blood group determining isoagglutinogen (A or B) it is usually of another type found in the red blood cells This particular antigen is known as the Rh factor because it was first found in Rhesus monkeys If a woman who has no Rh factor in her blood cells (Rh negative mother) conceives by a man who has (Rh positive father) *75–100* per cent of her offspring will have the Rh factor in their red blood cells (be Rh positive) In about *2* per cent of Rh negative mothers the Rh factor will pass from the Rh positive fetal blood into the maternal circulation causing the devel opment of antibodies to this factor in the mother s blood serum These antibodies pass into the fetal or infant blood cause hemolysis of the Rh positive infant s red cells and are thus responsible for the development of symptoms of erythroblastosis

The test to determine Rh positivity or negativity is generally outside the scope of office procedures and should be performed in a competent laboratory In ordering transfusion for an infant with erythroblastosis (one of the chief therapeutic measures) the *only safe procedure is to use a donor who is Rh negative* An Rh positive donor has Rh *antigen* in his red cells and thus will contribute more red cells for lysis by the antibody which the child has received pas sively from the mother The mother s Rh negative blood may not be used because it contains the lytic *antibodies*

In addition to erythroblastotic infants about *15* per cent of all patients requiring blood transfusion are Rh negative Once these Rh negative persons receive a transfusion of Rh positive blood they may develop anti Rh antibodies *All subsequent transfusions must then be with Rh negative blood*

There are at least three types or subgroups of the Rh factor (Rh Rh_1 and Rh_2) and in a small proportion of cases even a person who is Rh positive for one or two of these factors can *develop anti bodies to another Rh subfactor* In this way in exceptional instances red blood cells with one Rh subfactor may be hemolyzed by an Rh positive recipient who lacks and has become sensitized to the

particular subfactor And an apparently Rh positive mother may on occasion produce an infant with hemolytic disease if she conceives by a man whose red cells possess an Rh subfactor lacking in her own cells and to which she has developed antibodies

Transfusion of *75–150 cc* blood is the best therapeutic measure for erythroblastosis fetalis when the chief clinical manifestation of the disease is hemolytic anemia When there is little anemia but severe jaundice with imminent kernicterus an exchange transfusion (Wiener) is the treatment of choice It is *often lifesaving when given promptly* Administer blood whose *cells contain none of the factors or subfactors to which the mother may have developed antibodies* Whereas experts by employing laboratory technics may be able to demonstrate the absence of any Rh factor or subfactor in a given blood the safest procedure for the practitioner is to *give the mother a small transfusion of the presumably Rh negative blood* If there is no reaction within one hour it may be assumed that the cells of the transfused blood possess no antigen to which the mother and infant have antibodies and therefore the blood is safe to administer to the infant

When therapy *is urgently required the hour spent waiting for* the result of the biologic transfusion test in the mother may be utilized to administer to the infant plasma or physiologic saline or a suspension of red cells from the mother which have first been *carefully washed to remove all traces of possible lytic antibodies* The care of an erythroblastotic infant is a hospital procedure and should be under the direction of an expert in the field This brief summary is given to help form a basis for understanding the principles of treatment

It may perhaps be thought advisable in a particular case to determine whether or not a female patient is Rh positive since it may influence the selection of a donor if a transfusion is needed Indeed it might be advisable to include this information in the health *record of every female* child A handy technic using anti Rh serum in capillaries is applicable to office use It must be stressed again

that this test is not a routine office procedure The result of such a test should whenever possible be checked by a competent laboratory before transfusion is given The following firms supply the serum Directions accompanying the serum should be carefully adhered to

Gradwohl Laboratories Anti Rh Serum in 1 cc. bottles

Lederle Laboratories Inc Anti Rh Serum (Standard 85 per cent) in vials for 100 tests and in capillaries for 10 tests

Chapter Five

RESPIRATORY ALLERGIES

W C Spain

Introduction

BRONCHIAL ASTHMA hay fever and perennial coryza are classed as forms of respiratory allergy since their symptoms arise from allergic disturbances of the upper and lower respiratory tract In bronchial asthma the tissues of the bronchial tree are the site of reaction whereas in hay fever and perennial coryza the tissues involved are located in the nose nasopharynx paranasal sinuses and eyes The proximity—indeed continuity—of the tissues of the upper and lower respiratory tract may explain the frequency with which the symptoms of asthma hay fever and coryza seem merged in the same individual and result from the identical eliciting agent or agents

As a rule many allergic conditions of this group show a familial disposition are skin test positive and have demonstrable circulating antibodies (passive transfer or Prausnitz Kustner) They thus present the features which class them as *atopic diseases* (see Chapter 6)

Our use of the term atopy" departs somewhat from the historic meaning Originally it applied only to forms of allergy which were skin test positive and had circulating antibodies for these were supposedly the only forms having a familial predisposition. Our present use of the term

covers a group of clinical entities which often have a familial predis position but do not always have positive skin reactions or circulating antibodies

From the term respiratory allergy it might be assumed that the eliciting agent produced symptoms only on inhalation with inspired air This indeed does occur although only in about *one half* the cases the agent in these instances is an air borne substance such as pollen dust animal dander or vegetable powder In the remaining cases of respiratory allergy however the eliciting agent enters by other routes it may be absorbed through the intestinal tract following ingestion (foods or drugs) or it may be absorbed through the skin etc Products of infectious micro-organisms transported by lymph or blood from areas of infection to the sensitized bronchial tissues cause allergic disturbances in an unfortunately large number of cases

Any of these allergens—inhalant food drug and micro-organism—may also cause respiratory allergy through the artificial procedure of deliberate administration by hypodermic or other injection The administered allergens can then be carried by blood and lymph to the bronchial tissues Overdoses of allergens and of serums administered in diagnosis or treatment may thus produce reactions in the respiratory system

Respiratory allergy is not the same therefore as *inhalant allergy* since respiratory allergy refers to the reacting organs whereas inhalant allergy refers to the class of eliciting agents which are those generally inhaled Allergy to inhalants and food drug and bacterial allergies are all found as components of respiratory allergy

AGE

The age of the patient has some bearing on the incidence of the various types of respiratory allergy Bronchial asthma may occur at any age but those cases which appear *before age 3 are usually due to foods or infections* rarely to air borne substances Likewise hay fever and perennial coryza of inhalant origin rarely develop before

TABLE 12.—RESPIRATORY ALLERGIC ENTITIES: SKIN TESTS AND IMMUNOLOGIC PROCEDURES IN PROPHYLAXIS AND THERAPY

CLINICAL ENTITY	SKIN TESTS		PROPHYLAXIS		SPECIFIC THERAPY	
	Typ	V l	Typ	V l	Type	V l
Asthma 1 Noninfect e bronchi l	1 Scratch or intra cutaneous tests w th s spected inh led ingested or contacted alle gens read in 5–20 m n Response wheal and flare 2 W th phy c l agents (heat, cold)	*Generally of al e but may f l t s d cate cl n cal tens t vity (s e subst nc s g t e on sk n test m y be sp cific u s s b t nces el c t g pos tive sk n e s m y be n- no uous cl cally)*	Avo dance of and protection ag st inhaled i gest d and co t cted allergens	*G ne ally f alue*	Avo dance of and protection again t pro ed i haled in gest d a d co tacted caus l allerge s *plus hyposens t za* tion w th specific extracts	*Generally of gr t v l e*
2 Infecti e bronch al	No e		No e		Alle ation a d attempted removal of causat ve infection g rally located in upper resp r tory tract	*Gener lly of val e*
Coryza non seasonal or perenni l vaso-motor rhinitis	See no nfect ve *bronchial* asthma		See non nfective bronch al asthma		See non nfect e bro chial asthma	
H y fever	Scratch or intracu ta eous tests w th suspected i haled pollen antigens	*Generally of great alue*	No e		A o danc of pollen exposures when pract cable hypo-sens tization w th specific pollen extr cts	*Of g eat value*

age 3 *After adolescence foods become of less and less importance as eliciting factors infections become more and more important, while inhalant factors retain their allergenic status* The situation here is closely analogous to that in atopic dermatitis (p 263) When the age of onset of respiratory allergy is 50 years or over the elicit ing factor is almost always infectious

SEASON

The respiratory allergies are influenced by the season of the year This is obvious in hay fever which is due to pollens present in the air only during certain months Inhalant forms of bronchial asthma arising from causes within the home such as dusts feathers animal danders are worse in the colder months when doors and windows are closed when dust forming and dust catching materials are more in use and when artificial heating agitates the confined air Bronchial asthma of infectious origin is usually worse in the winter season The influence of the immediate environment and the general geographic area on respiratory allergy will be discussed in the sections on asthma and hay fever

ASSOCIATION WITH OTHER CONDITIONS

Respiratory allergy frequently is associated with other forms of allergy Bronchial asthma rarely occurs entirely independent of allergic coryza while hay fever frequently has bronchial asthma as a complication Intestinal and cutaneous forms of allergy (atopic dermatoses) are often found in conjunction with the respiratory allergies

NECESSITY FOR EARLY TREATMENT

Even the mild and simple forms of respiratory allergy should be treated for such cases if neglected may acquire superimposed in fections of the upper and lower respiratory tract. Acute and subse quently chronic sinusitis and bronchitis become the chief complica

tions in respiratory allergy Secondary pathologic changes such as emphysema atelectasis and bronchiectasis occur The intractability of cases of hay fever, coryza and asthma often results from infections of the respiratory tract

Bronchial Asthma (Paroxysmal Allergic Dyspnea)

In most cases of bronchial asthma the diagnosis is self evident and the physician s diagnostic efforts center on the identification of the eliciting agents which are variable and specific for each case In direct contrast in other diseases the chief investigative effort of the physician is directed toward identifying the disease for the specific etiologic agent automatically becomes apparent on the establishment of the diagnosis

It is usually far easier to ascertain the presence of bronchial asthma than it is to identify and locate the particular eliciting factors for the possible eliciting agents of asthma are many and diverse They are found among air borne substances capable of being inhaled such as pollens dusts animal danders lints vapors fungi other micro organisms among foods of all categories such as milk egg meats poultry fish fruits vegetables beverages among bacterial allergens absorbed from infections usually of the upper respiratory tract and among drugs such as salicylates and barbiturates which although free from even traces of protein are capable of behaving as active often overwhelming excitants of asthma Since any asthmatic patient may have developed sensitizations not only from one but from a number of causes derived from the several groups the search for eliciting agents becomes a highly individualized problem Frequently this search demands the most exacting and meticulous methods of examination and presents problems so complex that usually they can be solved successfully only by the trained and experienced specialist Such complex cases are considered to be beyond the scope of the present text Only the simpler forms of bronchial asthma in which the causes are few and are demonstrable by cutaneous test and/or by clinical investigation are here considered

DISCOVERY OF ELICITING AGENTS

Methods —As in other problems in allergy the first diagnostic procedures should be a methodical exhaustive history a complete listing of clinical evidence and an evaluation of symptoms A thorough physical examination with attendant x ray and laboratory procedures is obviously essential in asthma Special attention should be directed to the condition of the heart, the circulatory system lungs pharynx and paranasal sinuses Asthma of cardiac, renal thymic and mediastinal pressure or of other origin must be ruled out by diagnostic procedures beyond the scope of this text. Only when these procedures have been completed, and skin testing still seems necessary should skin tests be employed in an effort to deter mine the exciting agents

Either the scratch test or the intracutaneous test can be used in as certaining eliciting agents in cases of bronchial asthma in which *air borne or inhalant substan es* are culpable agents this type of test is satisfactory in only one half or less of the cases in which foods are the excitants and is *not generally indicated* or useful *when bac terial agents or drugs are responsible* For the reasons given on page 27 the nonspecialist may prefer the scratch test technic

A *comprehensive questioning* of the patient usually *excels all other methods* and will often furnish clues when skin tests are negative

HISTORY TAKING IN BRONCHIAL ASTHMA

History taking in bronchial asthma is useful not so much for the diagnosis of the clinical ailment, but for the identification of the type of asthma, the evaluation of the severity of the symptoms and the discovery of the eliciting factors A comprehensive meticulously taken history should provide

1 Advance warning *before* skin testing is attempted, of any peculiar or unusually pronounced degree of sensitization to aller genic substances whether inhalant, food or drug By uncomfortable

experiences the patient has usually learned the eliciting allergens which cause violent reactions

2 Corroborative evidence, after skin testing has been completed to establish the significance of positive test reactions

3 Identification of active allergens (often foods or drugs) when skin testing does not prove helpful

The history of a case of bronchial asthma should be taken in as much detail as possible Since the patient is ready and anxious to tell of his present discomfort the details of the present attacks should be recorded first

PRESENT HISTORY —Although no two cases of asthma present the same symptoms the following questions are generally important in relation to the present attack.

1 Are the attacks mild, or are they so severe that they are incapacitating? *Do they prevent you from continuing your usual routine?*

2 On what date did the last attack begin? How long did it last? Was it modified or stopped by medication?

3 What medications are needed to lessen or to check the attack? (Relief from occasional small oral doses of a drug implies the presence of a mild asthma. Repeated doses of epinephrine by injection or by inhalation imply the presence of a severe asthma.)

4 Is there loss of weight, bronchitis or an elevated temperature with the attack? (If so infection is suspected as a cause)

5 Is there a persistent coryza, sneezing irritation and itching of the eyes associated with the attacks? Or headaches urticaria, or nausea and vomiting? (If the former triad of symptoms is present an inhalant cause is suspected if the latter symptoms a food cause)

6 How often do the attacks recur? (Infrequent attacks suggest infrequent contact with the eliciting agent.)

7 Are they isolated with periods of complete freedom between bouts or is there continuous discomfort with wheezing or cough on exertion? (Paroxysmal attacks suggest that the cause such as inhalant or food, is encountered infrequently Continuous asthma suggests constant exposure to the cause which may be a common food or an infection.)

8 Are the attacks related to the season of the year or to a day of the

week? (The occurrence of asthmatic attacks in the winter season suggests certain causes for example a bacterial agent occurrence in the summer suggests that pollens may be the cause If the attacks occur consistently on the same day of the week, the activities and diet of that day should be suspected)

9 Do the attacks disappear while in some locations only to reappear with regularity while in others? (Asthma which occurs only in certain places is usually caused by agents encountered only in such an environment, e g dust from a patient s own mattress the dander of his pet dog If the asthma is nonenvironmental, suspected factors are those with which the patient is constantly in contact such as foods or infections)

10 Are associated conditions suspected of being allergic, such as atopic dermatitis urticaria, angioneurotic edema, hay fever headache mucous colitis purpura? (Bronchial asthma is frequently associated with other clinical allergic forms the etiologic diagnosis of which may aid in solving the asthma problem.)

PAST HISTORY—The following questions are generally important in relation to the patient s past

1 When the asthma first developed did it differ in any of the characteristics now noted? In other words would there have been different answers to any of the foregoing questions? (An asthmatic condition frequently becomes more severe and changes from paroxysmal to continuous seasonal to nonseasonal, environmental to nonenvironmental, as eliciting agents increase in number and severity or are replaced by more persistent ones)

2 In infancy or childhood did you suffer from eczema or dermatitis? Croup ? Food allergies? (Bronchial asthma may be the clinical form replacing the original allergic manifestations although the causative factor may remain the same)

3 Is there a history of severe acute or chronic upper respiratory infections such as sinusitis tonsillitis bronchitis? Is there a history of pertussis measles scarlet fever? (The occurrence of any of these conditions immediately before the onset of the asthma suggests the presence of a bacterial allergen)

SUSPECTED CAUSES—The patient may furnish many whimsical and false ideas regarding the causation of his asthmatic attacks Im

portant information however may be gleaned from such data particularly in instances in which the asthmatic attacks occur so promptly and so sharply after contact with the eliciting agents that the connection is obvious

Exposures to Inhalant Substances—The *bedroom* is the source of many of the important air borne allergens The patient should be questioned about the equipment and furnishings used by himself as well as by any roommate

Mattresses pillows boxsprings must be investigated. It should be determined whether these contain the hair of the horse hog cow rabbit or goat wool cotton kapok rubber latex Are *comforters* filled with down mink tails wool cotton or kapok?

Upholstered bedroom furniture should be considered A couch chaise longue daybed or the padded head boards of a bed should not be overlooked

When the patient s knowledge of the nature of the materials involved is doubtful small samples of each material placed in separate envelopes and properly marked should be submitted to the physician for identification Or better still the physician should inspect the patient s home and its furnishings

The occupations and hobbies of the patient and his immediate family must be noted Exposure to dust animal danders cereal flours chemicals etc must be ascertained

Floor coverings large rugs or carpets extending under heavy furniture or attached to the floor are seldom removed and cleaned hence are dust catchers

The patient should be questioned concerning exposures to horses dogs cats rabbits other animals and pets Does he own any of these? Are any of these in his immediate environment? Are any attacks related to these exposures?

The use of *sprays and chemical fumes* for insecticides moth preventives or disinfectants should be noted

Exposures to Foods—Food allergens which cause bronchial asthma often may only be identified through careful and meticulous

questioning This is exceedingly time-consuming except for infants and the very young whose diets are limited There must be obtained in detail from the patient a knowledge of his dietary habits his whims fads and excesses Such data are of prime importance especially in two contrasting forms of food allergy In the *first* the patient is so highly sensitive that he knows that exposure to certain food substances is followed usually immediately by symptoms which are severe even disastrous A foreknowledge of such situations and of the causative factors will enable the physician to save the patient from the dangerous effects which might follow skin tests with the extracts of the offending materials In the *second* form the patient develops symptoms of asthma only after an interval of hours often as many as 48 or 72 In cases with such a prolonged reaction time neither clinical knowledge nor positive food tests are available to aid in the diagnosis The physician must rely on a careful inventory of the patient s diet and on trial and error procedures (p 59)

When questioning a patient on his exposures to foods all items of his menu must be suspected and investigated However certain food substances are most important because of their common use and their ability to produce severe reactions These foods are

Egg	Milk	Nuts seeds as mustard seed
Wheat	Seafood	Chocolate

Each variety of meat poultry cereals fruits and vegetables must be considered A patient may be sensitive to one variety of meat or cereal but not to others Coffee tea and alcoholic beverages must not be overlooked

To ascertain what food or foods are in the first mentioned form of food allergy i e when the symptoms severe and explosive follow promptly on contact the following questions should be asked

1 What food through the inhalation of its odor and without ingestion, produces asthma, coryza, sneezing?

2 What food, through contact with the unbroken skin and without ingestion, produces asthma pruritus urticaria or dermatitis?

3 What food when ingested produces sudden violent effects of

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Exposures to Foods—Food allergens which cause bronchial asthma often may only be identified through careful and meticulous

of the family may be of little practical value in the treatment of bronchial asthma Such a positive history suggests however that the asthmatic condition under study is in all probability of the *atopic* group, in which skin testing will be helpful and the causative factors more easily identified

History Outlines —History forms with blank spaces designed for the insertion of answers to routine and stereotyped questions are not generally useful in a clinical condition as variable in characteristics and in symptoms as bronchial asthma It is much more satisfactory to record the history on a completely blank page using an outline of the important points to be considered as a guide for thoroughness and order The following outline is used for this purpose in the New York Post Graduate Allergy Clinic

A Present condition
  Last attack date?
    intensity?
    medications used?
    duration?
    frequency?
    associated symptoms
      a) allergic?
      b) infective?
  Paroxysmal or continuous?
  Seasonal or nonseasonal?
  Environmental or nonenvironmental?

B Past condition
  Age at onset of asthmatic condition?
  Original character of attacks?
  Associated conditions
    a) allergic?
    b) infective?

C. Causes known or suspected
    a) inhalant analysis
    b) food, drug analysis

D Family history

SKIN TESTS

Substances producing asthma by being inhaled (the inhalants) and by being ingested (the foods) may readily be prepared into either dry or fluid extracts Intracutaneous or scratch tests may be performed with these the scratch test may be preferred by the non specialist (p 27)

In the patient with bronchial asthma caused by inhalants skin tests for immediate or wheal reactions by the scratch method with these extracts may be expected to be successful in almost every instance But in the patient whose asthma is due to the ingestion of foods positive results with the offending foods can be expected in only *about one half* the cases These positive results usually occur in individuals in whom *asthma promptly follows the ingestion of the food When several hours intervene between cause and effect, consistently negative results by skin testing can be expected* Such negative findings on skin test also occur regularly in those cases of asthma due to bacteria or to other micro organisms and are the rule in practically all cases due to drugs

When foods are suspected but are negative by skin test only by experimental methods (p 59) is there any possibility of identifying the food factors *At least one third of all cases of bronchial asthma in both the child and the adult have as a sole or as a complicating cause a sensitization to micro organisms located primarily in the upper respiratory tract especially in the paranasal sinuses* with additional possible infection in the teeth tonsils nose nasopharynx and pharynx This complex bacterial involvement may account for the difficulty in obtaining successful treatment in certain cases of asthma *Any case of respiratory allergy which fails to show improvement under careful specific treatment indicated by history and by test should be suspected of possessing such an infective factor* These cases (especially the chronic type of asthma) are essentially the responsibility of the rhinologist and from his efforts these patients should expect the major portion of whatever relief they may obtain

Obviously such cases should be placed in the hands of a rhinologist as early as possible

Materials for Testing—The following list of *nonseasonal inhalant* extracts has been approved by the Committee on Standards of the American Academy of Allergy and is considered sufficiently complete for the ordinary testing for sensitization to inhalants

House dust	Rabbit dander	Tobacco
Dog dander	Orris root	Pyrethrum
Cat dander	Cottonseed	Silk
Horse dander	Kapokseed	Goat dander
Poultry dander (chicken duck goose)	Flaxseed	Alternaria

Additional allergens are added as indicated by the locality and the season. Extracts of *timothy plantain* and *ragweed* are added for diagnosing pollen asthma in the areas east of the Mississippi River In the eastern United States asthma due to the inhalation of *mold spores* is worse in the late summer but is not strictly seasonal. In other areas other pollens and fungi other than Alternaria are important (see hay fever p 218 The extract of yeast is not included in the approved list of nonseasonal inhalant extracts for it is rarely important as an excitant.

The following items are approved by the Committee on Standards of the American Academy of Allergy as ample for skin testing in most problems in food allergy

	SERIES I	
Milk	Chicken	Tea
Egg	Pork	Coffee
Wheat	Beef	Chocolate
Rice	Lamb	Mustard
Rye	Codfish	Coconut
Oats	Halibut	Peanut
	SERIES II	
Orange	Strawberry	Corn
Grapefruit	Onion	Spinach
Banana	White potato	Cucumber
Peach	Celery	Lima bean
Prune	Cabbage	Pea
Apple	Carrot	Tomato

Skin tests both scratch and intracutaneous with the extracts of various pathogenic micro-organisms of respiratory type have been advocated as a means of determining the causes of bacterial allergy But it is generally agreed that the *micro organisms causing infective forms of allergy*

cannot be identified by means of the skin test for immediate or urticarial type of response The delayed or *tuberculin type* reaction with the oc currence after 24 hours of erythema infiltration or a papule at the site of the test may often indicate the degree of the individual s *cutaneous sensitiveness* to the bacterial allergens involved Whereas such a result may not always be diagnostic it certainly affords a fairly satisfactory rough index of the patient s reaction to those particular allergens Such reactions thus serve as a guide to any necessary adjustment in dosage regardles of whether a stock or an autogenous respiratory vaccine is involved

All of the extracts mentioned as well as many others which may be indicated for testing in particular instances are available from a number of pharmaceutical firms whose allergenic products have been accepted by the Council on Pharmacy and Chemistry of the American Medical Association The following descriptions of these allergens together with the methods of preparation and standardization of potency are given in *New and Nonofficial Remedies 1946* Unfortunately there is a great diversity in the methods of designating potency (p 232)

Arlington Chemical Co powdered inhalant food and bac terial material in vials also 1 100 1 500 and occasionally inte mediate dilutions in 1 2 3 5 and 10 cc vials Packages are supplied containing one each of four concentrations 1 10 000 1 5 000 1 1 000 1 500 of the foods and inciden tal extracts (including yeast extract) 1 100 000 1 10 000 1 1 000 and 1 500 of the epidermals concentrations of 1 500 and 1 100 and occasionally intermediate dilutions are mar keted in 5 and 10 cc. vials also vials containing 15 25 or 50 mg of the powdered protein material for the scratch test and 1 cc. and 3 cc vials containing a 1 500 solution of the protein material for intracutaneous testing

Endo Products Inc house dust concentrate for diagnosis in vials containing 1 cc of a 1 200 solution of the original ma terial in 50 per cent glycerin, with accompanying applicator

Hollister Stier Laboratories food animal epidermal and other protein extracts for diagnostic purposes in 1 cc. ampules fitted with capillary tube and rubber bulb

Lederle Laboratories Inc. 6 cc vials of aqueous extracts of the inhalant and food substances The inhalant extracts and some foods such as the nuts are standardized on the basis of total nitrogen content per unit volume and supplied depending on the extract, in strengths of 0 001 0 01 and 0 1 mg of the nitrogen per cc Certain others which in the judgment of the makers do not lend themselves to such standardization are supplied as undiluted 1 10 dilution and 1 100 dilution. These aqueous extracts in proper dilution, may be used for scratch and intracutaneous methods of testing The same extracts glycerinated and concentrated are also supplied in single test capillary tubes for use by the scratch method

Parke Davis & Co protein extracts from plant, food, bacterial and other proteins in the form of a paste in collapsible tubes containing 1 5 Gm of material designed for the diagnostic scratch test. Supplied in similar form are tubes containing mixtures of equal parts of two or more protein extracts selected for combination on the basis of their immunologic class relationship

Wyeth Inc. diagnostic aqueous extracts of inhalant and food proteins for use by the intracutaneous method in 1 cc. size cartridge ("Tubex") vials accompanied by a cartridge syringe and sterile needles The extracts are standardized on the basis of total nitrogen content per unit volume and are supplied depending on the extract involved in strengths of 0 0005 0 001 0 005 0 01 and 0 05 mg of total nitrogen per cc. House dust extract i supplied in a 1 10 dilution and horse serum in a 1 100 dilution

TREATMENT (IMMUNOLOGIC OR SPECIFIC)

Methods—All substances suspected or identified as eliciting agents by history and/or by skin test should whenever possible be remove from the patient s environment (pp 69 ff) These measures alon will be sufficient in the simpler cases When avoidance or great re duction of exposures is impossible owing to the character of th excitant an attempt may be made to increase the individual s toler ance to the eliciting agent This may be attempted through *sub*

cutaneous administration provided the eliciting agent is an inhalant substance amenable to injection therapy (p 79)

Materials for Injection Therapy—The extracts of the following non seasonal *inhalant* substances are used for specific injection therapy *Food extracts are not thus employed*

House dust	Cat dander
Orris root	Rabbit dander
Poultry dander (feathers)	Horse dander
	Goat dander
Dog dander	Alternaria and other fungi

As a rule though not without exceptions, asthma elicited solely by pollens is present only during the pollen seasons Spores of fungi produce nonseasonal asthma, but this is usually worse during the late summer and early fall (August–September) at the height of the spore season. (These forms are discussed in the section on seasonal allergic coryza.)

The following inhalant extracts are prepared by several organizations whose products are listed and described in N.N.R. 1946

Arlington Chemical Co inhalant extracts in 5 cc vials in concentrations of 1 100 000 1 10 000 1 1 000 and 1 500 Concentrations of 1 500 and 1 100 and occasionally intermediate dilutions are also available in 5 cc and 10 cc vials

Endo Products Inc house dust extract in treatment sets of four 10 cc. vials containing respectively slightly more than 1 cc of a 0 0025 per cent, 0 025 per cent, 0 25 per cent and 2 5 per cent dilution of the original extract in glycerosaline solution (50 per cent glycerin) and four 10 cc. vials of diluting fluid. The house dust extract is also supplied in maintenance treatment packages bulk treatment packages and special treatment packages

Lederle Laboratories Inc. inhalants in 6 cc vials in buffered saline dilutions representing 0 00001 0 0005 0 001 0 01 0 05 and 0 2 mg. of nitrogen per cc. depending on the extracts involved

Abbott Laboratories fungous extracts in 2 cc., 5 cc. and 30 cc. vials of Alternaria Aspergillus Cephalothecium, Hormodendrum, Monilia, Penicillium, corn smut, yeast. Each cubic centimeter of extract represents 0 05 Gm. of dried fungous material.

Results—Whenever the exposures to eliciting agents *cannot be avoided or materially reduced,* the result of the treatment of bronchial asthma is *less satisfactory* Inability to reduce exposures to the inhalant or food allergens may be due to the nature of the eliciting agents to the patient's lack of co-operation or to other factors Incomplete identification of eliciting agents by history or by test and injection therapy which is inadequate in dosage in duration or in comprehensiveness are further causes of poor results in the treatment of asthma As a rule *an 80 per cent lessening of the severity and frequency of the attacks can be anticipated in the simple uncomplicated cases which have been adequately treated with specific hyposensitizing injections* This degree of improvement cannot be maintained however unless the patient continues to follow carefully the rules laid down regarding changes in his environment and in his diet The development of such complications as an active sinusitis or other upper respiratory infection may prevent the patient from obtaining a satisfactory result.

Contraindications and Dangers of Specific Hyposensitizing Injections—It must always be remembered that exposure of the specifically sensitized individual to excessive amounts of active allergenic substances whether clinically or by injection may produce general or constitutional symptoms Caution must therefore be exercised in the administration by hypodermic injection of the allergenic extracts *Dosage should always be conservative especially in children* and the schedules supplied by the manufacturer for his product are to be followed in most instances In cases of ordinary sensitiveness (ascertained by the clinical history and the degree of positive response to skin test) *it is a safe rule to give intracutaneously an initial injection of no more than 0 02 cc of the lowest potency of the indicated inhalant extract supplied by the manufacturer* Subsequent increases and the length of interval between injections should be determined by the degree of local reaction resulting immediately or within 24 hours of the injection (p 81) Usually the *injection may be given at five to seven day intervals the doses increasing 0 1*

cc each time until a ceiling of 1 cc is reached The physician must decide whether subsequent treatment should consist in repeating the 1 cc ceiling dose from this vial or in continuing the increases by substituting injections from a vial of extract of greater potency The resulting decision depends both on the degree of sensitiveness of the patient and the effectiveness of the treatment

Length of Treatment—This depends not only on the degree of sensitiveness of the patient and the effectiveness of the treatment, but also on the nature and complexity of the eliciting agents For example if the patient s asthma is caused by the presence in his home of a dog or a cat it may be necessary to treat him with hyposensitizing injections of the *animal* dander extract for only four to six weeks after removal of the animal—the length of time usually necessary for traces of animal hair to disappear from the home If however the patient is forced to visit in homes where there are animals to which he is sensitive it may be necessary to continue the specific hyposensitizing injections for an indefinite period. Such lengthy treatments may also be necessary when the eliciting factor cannot be completely removed from the environment, as in the case of house dusts If *the asthma is of pollen origin* the schedules for treatment will be the same as those described for the treatment of hay fever

The desensitization produced is usually only *partial* i e a *hypo* sensitization This becomes evident especially if the offending factor has not been removed from the environment Thus *an asthmatic patient sensitive to dogs will persist in having attacks despite injection treatment with dog dander extract unless the animal is removed* The purpose of the injections is to protect the asthmatic patient against occasional or chance contacts with dog And if at all possible it is only after many months of continued hyposensitizing treatment that the individual can be rendered somewhat resistant to continued exposures to the eliciting allergen *Brief periods of injections are rarely sufficient to produce adequate lasting protection often several years of uninterrupted injections are necessary* with doses

gradually larger and intervals between injections gradually longer

The hyposensitizing treatment may consist of several different allergenic extracts given simultaneously (p 81) Thus the extracts of dog dander house dust and ragweed may all be given at the same time but preferably in separate syringes so that any local reaction which occurs may be noted and attributed to its proper source

A form of nonspecific therapy which may perhaps be considered immunologic is the recently introduced use of antihistaminic drugs Although it is still too early to sum up the results accurately the administration four to eight times daily of 25–50 mg Pyribenzamine (Ciba) or Benadryl (Parke Davis) appears to have a significant beneficial action in about 30 per cent of all cases of asthma

WARNING

To avoid severe even lethal effects in testing the very sensitive patient employ the extracts of the following allergens with *greatest* caution and respect

Cottonseed	Egg
Flaxseed	Mustard
Kapokseed	Nuts
Glue	Horse serum
Fish	

Always complete the history before testing

Hay Fever (Seasonal Allergic Coryza, Pollenosis)

The term hay fever is restricted to allergic coryza (rhinitis conjunctivitis) caused by sensitization to pollens It should not be applied to coryza resulting from sensitization to dusts epidermals fungi or other inhalants or to coryza caused by sensitization to foods or drugs Nonseasonal allergic coryza is considered separately Hay fever occurs both in adults and in children The following discus

sion applies also to *pollen asthma* which may occur either with hay fever or alone

ELICITING AGENTS—*Seasonal and Geographic Occurrence*—Hay fever cases readily group themselves according to the seasons of occurrence of their pollen causes into the *spring* the *summer* and the *fall* varieties A patient may have any one or any combination of these three varieties Within the continental United States there are usually only minor variations of the seasonal limits of these three groups The geographic localization can determine major variations in the pollens involved especially in the fall group

1 In the United States the season for the *tree pollens* responsible for *spring hay fever* extends from about *mid March to June 1,* beginning somewhat later in the North and somewhat earlier in the South where it lasts somewhat longer In the far South especially in the southernmost portions of the states fringing the Gulf of Mexico and in coastal California—areas where the last killing frost occurs not later than March 1 if at all—the tree season may begin in *January and last through May*

2 The season for the *grass pollens* responsible for *summer hay fever* is even more variable than the tree season In the northern states it extends from *mid May to mid July* but the season lengthens the farther south one goes Along the Gulf of Mexico and in coastal California the grass season begins in *April and ends in September* or later Indeed in the southern portions of Florida Texas and coastal California the grass season extends practically *throughout the year*

3 The season for the *pollens* responsible for *fall hay fever* extends from *mid August to October* especially in the areas in which *ragweed* is the principal factor i e in the eastern two thirds of the United States In the North where frosts occur early the season may be shorter in the far South the season may extend well *into October* In southern Florida ragweed pollen appears in *May and lasts until October,* whereas in southern California ragweed pollen may appear in *July and last until November* The amaranths chenopods and sages producers of pollens important in the Plains States

TABLE 13—Pollens Important in Eliciting Hay Fever

ZONE I EASTERN HALF OF UNITED STATES

Spring

T s

Ash (Fraxinus amer cana)
Beech (F gus grand folia)
B rch (Betula)
Elm (Ulmus)
Oak (Que cus)
H ck ry (Carya ovata)
P plar or cotto wood
(P p lus delto des)
W lnut (J glans nigra)
Pec n (Cary pec)[b]

Summer

G as s

Timothy (Phleum
pratense)
Orcha d (Dactylis
gl merata)
Jun or Kentucky blue
(Poa praten is)
Redtop (Agro tis
pal stris)
Bermuda (Cy odon
dactylon)
Johnson (So ghum
halepens)
E gli h pla tain
(Plan ago l ceol ta)
So rel (Rumex
acetosella)

F ll

Ragwe d f m ly

G ant ragweed
(Amb a trifida)
Dwarf gweed
(Ambro a elatior)
Cockl b (Xa h m)

ZONE II PLAINS STATES

Tr s

A h (Fr ame ca)
B ch (Betula)
Elm (Ulmus)
O k (Que cus)
H kory (Carya o ata)
P pl o c tronwood
(P p l s d lto des)
W llow (Sali)

G as s

Timothy (Phleum
prat se)
J n o Ke tucky bl e
(P p ten s)
E gl h planta n
(Pl go la ceolat)

Ragw d f m ly

Giant agweed
(Amb rifid)
Dw rf ragweed
(Ambro a l t)
Wes rn ragweed (Am
bros a p lostachya)
Cockl bur (Xa h um)
B rweed m rsh ld r
(I a x th fol)
F lse agweed (Fra
se ch carp)
Wormwood or ges
(Artem s)
3–7 v et es

Chenop d f m ly

Ch pod aceae
R t th stle
(S lsola pestif)
B rn g bush
(Koch copa)
Lamb s-quarters
(Ch pod um
lbum)
Am ranth ea
P gweed (Amar
thus retroflexus)

A less mporta t pollen
N rth of th Oh o Ri
[b] So th of th Oh o Ri e

TABLE 13 —CONTINUED

ZONE III SOUTHWESTERN STATES

Spring	Summer	Fall
Trees	*G asses*	*Ragu eed f m ly*
Ash (Frax nus mer can)	Berm da (Cy odon d ctylon)	B rweed m rsh elder (Iva x th fol)
Popl r o cottonwood (Populus d lto des)	J hnson (So ghum hal pe)	*Chenop d fam ly*
Willow (S lix)	Sud n	Ch pod aceae
Pecan (Cary pecan)		Russ an th stle (Salsola pest fer)
Mounta n cedar (J n perus s b n des) †		Bu g bu h (Kochi scoparia)
Mesquite (P osop s juliflo) ‡		Amaran h ceae
		Palmer s Am ranth (Ama nthus palm)

ZONE IV PACIFIC STATES

Tre s	*G ass s*	*R g eeds*
Alder (Alnus homb fol)	O chard (D ctyl s glome ata)	West n ragweed (Am bros a ps losta hya)
O k (Quercu dumosa)	J ne or Ke tucky bl e (Poa pratens s)	False r gweed (Fr se a acanthicarpa)
Cotto wood (Populus f emont)	Ry or w ld ry (Flym s cond tus and tr t co des)	Artemi ge us
Wal t (J glans n gra and cal forn ca)	Ray or ry (Lol m peren e and mul fl rum)	S gebrush (Artem s a tridentata)
Plat plane t ee w te n sycamo e (Plata us racemos)	V l et (Notholcus la tu)	M gwort (Artemis a vulgaris)
	Bermuda (Cy odon d ctylon)	*Ch opod f m ly*
		Red oot p gweed (Ama ra hus retroflexus)
		R s n th stl (S lsol Kal ten ifolia)

A less mporta t pollen
† Only in central d so thern Te s
‡ Only n west Texa

and the Southwest occur from *July through September*, and *even through October* in the more southern areas

Pollens important in eliciting hay fever[1] are given in Table 13 No pollens of little or of strictly local importance are included. The division of the pollens into *spring summer* and *fall* according to their periods of pollenation is necessarily arbitrary and approximate This division cannot be made more clearcut or definit- the seasonal limits fluctuating with variations in climate

[1]The author is indebted to Drs Donald Cunningham of Denver Harvey Black of Dallas and George Piness of Los Angeles for information and lists of pollens most important in the Plains States the Southwestern States and the Pacific States respectively

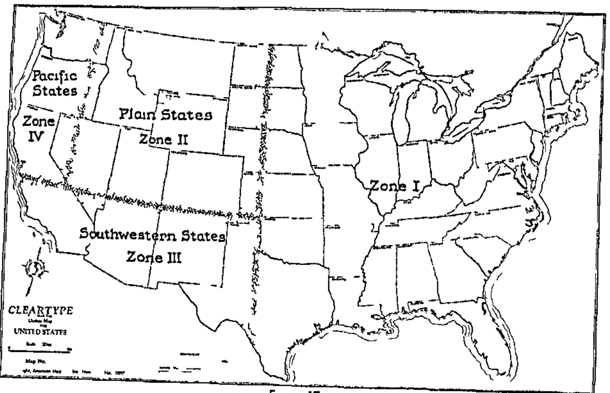

Pacific States
Zone IV
Plain States
Zone II
Southwestern States
Zone III
Zone I
CLEARTYPE
UNITED STATES

Figure 17

Figure 17 shows the major divisions of the continent that are important in determining variations in pollenation The zones as established on the map are schematic and somewhat arbitrary Zone I includes the entire eastern half of the continental United States from the Canadian border to the Gulf of Mexico Its eastern boundary is the Atlantic Ocean and its western boundary an imaginary line roughly parallel to the Mississippi River which bisects the states of North Dakota South Dakota Nebraska Kansas Oklahoma and Texas Zone II to the west of zone I extends to a line roughly parallel to the Pacific Coast and extends from the Canadian border to the northern border of Arizona bisects Washington and Oregon and reduplicates the eastern border of California Zone III includes the western half of Texas all of New Mexico and Arizona and the southern fourth of California Zone IV includes the western halves of Washington and Oregon and the northern three fourths of California

Although botanically there are many species of grasses some of which are peculiar to certain areas of the United States their pollens appear to have identical biologic effects on the grass sensitive individual Apparently because of certain powerful allergenic *common denominators the extract of any grass may be used for diagnosis and treatment in the patient with any type of grass hay fever Timothy and orchard* pollens are most often used for these two are abundant and most easily collected The most common grasses in the United States are timothy orchard sweet vernal blue Bermuda and Johnson grass

In a manner similar to the various grass pollens the pollens of the several *ragweeds* seem to have certain common denominators i.e ingredients with an apparently identical allergenic effect In this group are high low and false ragweed and also the less important southern and western ragweed

Allergic coryza due to mold spores is frequently confused with hay fever since the spores although occurring at all seasons are *more prevalent in the warmer months from May to October*, and usually reach their peak in *August and September* Some cases of

seasonal coryza, therefore may be due to spores alone or to both spores and pollen Of chief allergenic importance are the spores of Alternaria Hormodendrum Aspergillus and Penicillium The spores of grain smuts such as corn smut and rusts have been described as causing respiratory allergy

POLLEN ASTHMA

In bronchial asthma due to pollens etc, the materials for specific treatment are those used in hay fever treatment

DISCOVERY OF ELICITING AGENTS

HISTORY TAKING IN HAY FEVER

The history in hay fever is usually more simple and more brief than that taken for bronchial asthma It should provide the following points of information the seasonal limits of onset and of cessation of symptoms the age of onset of the hay fever the presence of a complicating bronchitis sinusitis or asthma a description of the severity of the attacks and of any local or constitutional reactions resulting from previous therapy the presence of any associated allergic condition such as nonseasonal coryza, urticaria or gastrointestinal allergy

A knowledge of the seasonal limits will at once classify the patient s hay fever as being of the spring summer or fall variety or some combination of them even before skin testing with the pollen extracts *This narrows the choice for the initial testing to extracts of those pollens known to be present during the season or seasons specified* At subsequent investigative visits tests with the extracts of pollens occurring at other seasons should be made and any positive reactions noted in order to learn the possibility of the patient s acquiring additional types of hay fever

It is important to know the age of onset of the hay fever symptoms for cases of *long standing are more likely to have acquired complicating sinus or bronchial infections* The presence of such respiratory infections should be known since they provide a handicap to successful therapeutic results A foreknowledge of the presence of nasal polyps a deflected septum hypertrophied turbinates or

adenoid tissue will permit an attempt to correct such conditions well before the advent of the pollen season

There should be a complete description of the severity of the at tacks of hay fever Itching of the eyes and nose occurs in most cases Itching of the soft palate or auditory canals usually suggests severe hay fever The intensity and duration of the paroxysms of sneezing the presence of cough or wheezing the development of marked las situde or fatigue indicate severe forms of hay fever The patient should be questioned as to any local or general reactions developing after previous testing or treatment with pollen extracts

Patients with hay fever frequently are disturbed by associated allergic complaints The presence of nonseasonal coryza due to dusts animal danders or foods should be investigated as well as the pres ence of bronchial asthma Neglected hay fever frequently encourages the development of asthma which at first may occur only during the height of the pollen season but eventually will appear nonseason ally as well

The patient should be asked concerning the presence of an allergy to foods *especially to melons grapes sweet corn and peaches* Such seasonal foods occurring coincidentally with the fall pollen season are responsible for increased symptoms in some cases Any known hypersensitivity to drugs such as *epinephrine cocaine, the salicyl ates, the belladonna group,* should be recorded for these are fre quently used in the treatment of hay fever

When the hay fever is complicated by the presence of asthma perennial coryza or atopic dermatitis the history must be extended to include the points of importance in those conditions

SKIN TESTS

In establishing the diagnosis in hay fever the verification of the presence of the clinical condition is only the first step Wide vari ations occur in the pollens which may be factors and in the individual patient s ability to tolerate pollen It is therefore important to *identify the offending pollens* and to appreciate the degree to which

HINTS TO THE HAY FEVER SUFFERER (AND TO THE SUFFERER FROM POLLEN ASTHMA)*

The symptoms of hay fever are caused by the pollens of certain trees grasses and weeds but there are a number of substances and circumstances which may aggravate the condition. Important among these are

Cultivated flowers cut and brought into the house where the pollen, usually sticky is able to dry sufficiently to become buoyant and air borne Plants growing in pots are usually harmless

Chemical fumes generally from lacquers paints gasoline naphthalene flakes camphor balls and other moth preventives insecticides sprays for rose bushes fruit trees and other vegetation, dry cleaning fluids fumigating gases leaky mechanical refrigerators and illuminating gas

Tobacco smoke particularly in crowded smoking rooms or railroad cars

Highly scented soaps and perfumes nail lacquer and lacquer remover hair tonics and lotions face and talcum powders shaving soap

Dusts from packing cases from freshly swept rooms from country roads Musty pillows and mattresses as in summer camps and cottages Lints from woolens or cottons

Strong light rays such as those in open fields at the seashore or at motion picture houses Wear dark glasses

Strong air currents sitting beside open car or train windows or on a porch

Swimming and diving particularly in fresh water

Overeating particularly of meat

Undereating weight reduction diets

Alcoholic beverages

Fatigue

Sinus conditions

* A form such as this [illegible] be handed to each patient with pollenosis.

they affect the patient This information is *necessary both for clinical appraisal and for therapeutic dosage* Patients vary greatly in their pollen dosage requirements The establishment of the degree of sen sitiveness is simple with the intracutaneous method of testing grad uations in skin response being observed when different dilutions of the same pollen extract are tested simultaneously on the patient When the scratch method is employed such delicate variations in re action are difficult or impossible to discover (p 25) The dosage of commercially prepared extracts most of which are used in con junction with the scratch test must be based on needs of the patient of average sensitiveness rather than on individualized or special requirements *The manufacturers therefore, hai e proi ided extracts and schedules designed for the patient with an ai erage degree of re action* Patients with *unusual degrees* of sensitiveness *either high or low offer problems in the indii idualized adjustment of dosage* It is advisable to refer such patients to the specialist familiar with the intracutaneous method of assaying the degree of sensitiveness

In the use of the standardized treatment extracts furnished by the manufacturers there is some risk that the routine doses based on the requirements of the patient with average sensitiveness may cause unpleasant even severe reactions in individuals with extreme sen sitiveness (See general or constitutional reactions p 90) For this reason the *initial dose of the standardized injection schedule adio cated by the manufacturers is i ery small being an amount found by experience to be tolerated safely by the great majority of patients*

The Council on Pharmacy and Chemistry of the American Med ical Association in recognition of the occasional patient having an extremely high degree of sensitiveness advises the *additional pre caution of a preliminary intracutaneous injection of 0 02 cc of the weakest solution of the therapeutic pollen extracts supplied by the manufacturer before any therapeu ic series is begun* There should be no reaction from the test either local or general except possibly a *slight wheal* at the site of injection

In the diagnosis of hay fever therefore these steps are necessary

1 *Venfication of the condition as hay fei er*

2 *Establishment of the type or types of hay fei er present (spring summer fall)*

3 *Determination by skin test of the pollens giving positn e reactions*

4 *Selection from the group of pollens found positn e by history and by test of those considered to be of chief importance*

5 *Estimation as far as possible of the degree of indn idual sen sitn eness by means of history and by degree of local response to pollen test and to pollen treatment*

The *ophthalmic test* may be employed in the doubtful case (p 54) whenever the clinical history is not substantiated by a pos itive reaction to the skin test The development of a positive reaction to the eye test in such an instance would justify treatment of the patient as one with pollen sensitivity

Materials for Skin Testing—Extracts of the pollens that have been mentioned and of many others important in local problems are available from a number of manufacturers whose products have been accepted by the Council on Pharmacy and Chemistry of the American Medical As sociation and described in *New and Nonofficial Remedies 1946*

The potency of pollen extracts and other allergenic extracts tends to diminish with age For this reason some manufacturers place expiration dates on their products and withdraw them as they become overage The physician should note such expiration dates and should preferably dis card any extract he has had *stored ei en in the icebox for oi er a year*

Pollen extracts for diagnostic use by scratch method (p 26) are generally available in capillary tubes each sufficient for one test. These are procurable from

Abbott Laboratories — Lederle Laboratories Inc
Arlington Chemical Co — National Drug Co
Hollister Stier Laboratories — U S Standard Products Co

Arlington Chemical Co in addition, provides 1 cc vials containing sufficient material for 15 tests and also provides dry pollens in vials containing 50 mg

TABLE 14.—POLLEN EXTRACTS FOR TREATMENT

MAKER	DESIGNATION OF POTENCY	TREATMENT PACKAGE SETS		CONCENTRATED EXTRACTS	
		Number of Vials	Potency of Extract in Each Vial	Amount in Vials	Potency
Abbott Laboratories	Wt. by vol. dilution method	4‡	1 10 000, 1 1 000, 1 100, 1 100		
Arlington Chemical Co	Wt. by vol. dilution method	5	1 10 000, 1 5 000, 1 1 000, 1 500, 1 100		
Barry Allergy Laboratory Inc	Wt. by vol. dilution method	4‡	1 100 000, 1 10 000, 1 500, 1 33 1/3	5 cc	1 33 1/3
Cutter Laboratories	Wt. by vol. dilution method	3	1 10 000, 1 500, 1 33 1/3	5 cc	1 33 1/3
Abbott Laboratories	Wt. by vol. units*	16‡	10, 20, 40, 70, 100, [illegible]00, 400, 700, 1 000, 1 500, 2 000, 3 000, 4 000, 5 000, 5 000 units	2 cc 5 cc	30 000 units per cc 30 000 units per cc
Hollister-Stier Laboratories	Wt. b[illegible] ol[illegible] t	4	10, 100, 1 000 and 10 000 [illegible]ts per cc plus 1 [illegible] 1 ster le distilled water for [illegible] also single [illegible]als of 1, 2, 5, 10 and 20 cc		

* Weight by volume unit represents the potency contained in 0.001 mg. of pure pollen.
† Total nitrogen unit represents the potency co[illegible]d [illegible] amount of pollen yielding 0.00001 mg. of total nitrogen.
‡ Extracts of grasses and ragweed only available in this form.
§ Extracts of [illegible]gweed only available in this form.

TABLE 14—CONTINUED

MAKER	DESIGNATION OF POTENCY	TREATMENT PACKAGE SETS		CONCENTRATED EXTRACTS	
		N t V ls	P t cy f E t t C e t e Vol	Am t I V l	P t y
Wyeth Inc	W t by ol u t	3—1 cc. cartr dge vi ls	100 1 000 6 000 20 000 d 20 000 ts pe cc	1 cc	5 cartr dg ls 20 000 u ts per cc
U S Stand rd Products Co	Wt by ol u t	3‡	100 1 000 10 000 un per cc.	5 cc ‡	20 000 un ts per cc.
		4‡	100 1 000 10 000 10 000 u ts pe cc	5 cc ‡	30 000 u ts per cc
Led l Labo t ies I	To al n toge t†	15‡	2 5 5 10 20 35 60 100 165 275 450 750 1 00 1 800 2 400 3 000 u ts	5 I sets	3 000 un ts per al 6 000 un ts per v al
		3—3 cc v als	100 1 00 20 000 ts per cc	3 cc ‡ (3 o 6 als)	0 000 u ts per cc
N o al Drug Co	T t l trog n u t†	3—5 cc. ‡‡	500 5 000 10 000 25 000 ts per cc	5 cc ‡ nd 15 cc ‡	2 500 5 000 10 000 25 000 u n pe c
				5 cc.‡ y nge pa k ge	10 000 a d 25 000 n ts per cc

Children under 6 years should rarely be treated, and the doses for those between 6 and 12 should usually be about half those given the adult with comparable sensitiveness

There are three forms of specific pollen therapy in general use

1 The most popular is the preseasonal *The preseasonal or prophylactic injection* schedule should be begun about *three months before* the anticipated occurrence of the symptoms and should be continued throughout the hay fever season at a dosage level established preseasonally Some manufacturers suggest stopping treatment at the onset of the season

2 In the *perennial method,* which may be used in selected cases the injections are not interrupted at the completion of the season s treatment but are continued at intervals of three to four weeks throughout the year until the following season The maintenance dose which is given throughout the year is that which was successfully achieved at the end of the season of prophylactic treatment. In order to be effective however this dose must be as high as is feasible and safe and must be among the larger doses advocated by the manufacturer of the product used Perennial treatment is best suited for the adult patient who has no more than average sensitiveness *It is contraindicated in children and in adults with a high degree of sensitiveness* In all cases pronounced local swellings at the site of the injection which last over 12 hours or constitutional reactions are usually contraindications to any continued attempt at perennial treatment

3 Seasonal treatment are satisfactory in most instances *Seasonal* or *phylactic* treatment may be begun *after* the onset of symptoms The doses are given at two to three day intervals with increases rarely exceeding during the season those embodied in the fifth or sixth dose of the commercial treatment set selected by the physician

Standards and Designations of Potency of Pollen Extracts— Unfortunately no precise tabulation of the injection therapy indicated may be presented here because *no method of standardizing*

allergenic extracts for potency has been generally adopted Con sequently the designation of allergenic activity and the specification of dosage vary with the manufacturer and product Of those manu facturers whose pollen extracts have been accepted for listing in N N R 1946 *eight utilize the weight by volume method to indicate potency and two employ the estimate of total nitrogen expressed in milligrams per cubic centimeter*

The majority of manufacturers use the term unit in designating potency but have *different basic definitions* of the term Four employ unit to designate the activity contained in 0 001 mg of pure pollen two to designate the activity contained in the amount of pollen extract yielding 0 00001 mg. of total nitrogen Four manufacturers make no attempt to employ the term unit

This deplorable lack of conformity and uniformity forces each manufacturer to establish his own plan of dosage and treatment, compelling each to be a law unto himself For this reason details in treatment more exact and more comprehensive than those fur nished cannot be given here Before attempting to use a particular product the physician *must consult the data of the manufacturer of the product selected and carefully follow* the directions furnished

Results of Specific Hyposensitization —For satisfactory results in *preseasonal or in perennial treatment of uncomplicated cases* it is necessary

1 To *identify* the chief offending pollens

2 To assay the *degree of sensitiveness* of the patient by other clinical data by reaction to skin tests and by responses to treatment

3 To *adjust the dosage* to the limit of tolerance

4 To give the *full complement of doses* recommended by the manufacturer of the product selected

If these requirements can be fulfilled a satisfactory diminution in discomfort from hay fever may be expected in the majority of uncomplicated cases

In *phylactic or seasonal treatment* a lesser degree of protection is obtained owing largely to the impossibility of achieving sub-

stantial doses because of the lack of a preseasonal interval of preparation and the difficulty of increasing dosage during the natural exposures to pollen during the pollinating period

Most hay fever patients show some improvement from any of the three forms of treatment even when underdosed In patients showing no improvement whatever despite comprehensive treatment there are usually complicating conditions such as chronic upper respiratory infections or nasal obstructions Such patients as a rule present problems which should be the concern of the specialist in rhinology

Contraindications and Dangers—The most common error in pollen therapy is to *overdose* rather than to underdose the patient The physician should be on the alert for evidences that the treatment is *in excess of the patient s tolerance or ability to accept the dosage*

A Local Reactions 1 Marked swelling erythema and itching at the site of the injection usually beginning *within* 10 minutes and sometimes lasting over 36 hours

2 Marked immediate reaction with erythema and itching not lasting 36 hours but resulting in immediate single or multiple wheals at the site of injection and involving an area 6–10 cm in diameter

B Focal Reactions Increased clinical discomfort (hay fever) for 24–48 hours following the injection with or without local reaction

C. General Reactions (see also p 90) 1 Immediate general or constitutional reaction consisting of acute often severe symptoms of generalized erythema pruritus angioneurotic edema bronchial asthma and/or hay fever Severe pelvic pain due to contractions of the uterine muscle may occur especially in the nulliparous woman Any combination of these symptoms may occur in varying degrees of severity the shorter the period between injection and reaction the more overwhelming the symptoms The immediate reaction follows *within* 15 minutes after the eliciting injection The extremely severe constitutional reaction usually is evident before the needle is withdrawn from the injection site

2 Delayed general or constitutional reaction has symptoms similar to those of the immediate type but is usually less severe and is rarely lethal It appears within 15 minutes to 24 hours following the injection

All general reactions require immediate steps which are specified on page 92 Should a general reaction occur reduce the amount of the next injection. If the reaction be *immediate and overwhelming* all further treatment may be *contraindicated* If the reaction be immediate but of less severity reduce the subsequent dose to 1/10–1/3 the size of the eliciting injection depending on the degree of severity of the symptoms If the reaction is delayed reduce the subsequent dose to 1/2–1/3 the size of the eliciting injection depending on the degree of severity of the symptoms

In both immediate and delayed types of general reaction subsequent increases in dosage should be attempted rarely and with circumspection

The new antihistaminic agents exert effects which are most promising in the treatment of pollen allergy Although there is insufficient experience for final evaluation the oral administration three to six times daily of 25–50 mg of either Pyribenzamine (Ciba) or Benadryl (Parke Davis) is reported to achieve significant benefits in the majority of hay fever patients

Nonseasonal Allergic Coryza, Perennial Allergic Coryza Vasomotor Rhinitis

SPECIFIC ELICITING AGENTS—*Seasonal* allergic asthma and *seasonal* bronchial asthma have the same group of excitants namely the pollens Similarly *non*seasonal allergic coryza and the *non*seasonal asthma with which it is often associated share common groups of allergens These include the inhalants except pollens (e g epidermals danders vegetable powders and fungi) foods drugs and bacterial allergens Therefore except for those which refer to pollens the remarks on eliciting agents of asthma also apply here It should be emphasized that cases of long standing

coryza especially in the adult are often not of proved allergic causation but rather are the *result of other mechanisms* such as endocrine imbalance or chronic upper respiratory infection associated with polypoid and hyperplastic changes in the membranes lining the nose and sinuses These disorders are always to be suspected when the investigation fails to disclose specific allergens Such conditions are often extremely difficult to help and are obviously the concern of the specialist and beyond the scope of the present discussion

DIAGNOSIS

Materials—These are listed in the section on bronchial asthma.

Methods—As always a comprehensive *history* should be the first step in diagnosis It should include a complete listing of the clinical evidence and an evaluation of symptoms

Skin tests may be made by the scratch or the intracutaneous method the former may be preferable for the nonspecialist. When doubtful evidence is obtained the ophthalmic test may be attempted

When tests are inconclusive or negative the *clinical tests* described in Chapter 1 should be made

TREATMENT

All steps in treatment are the same as those described for bronchial asthma

Chapter Six

DERMATOLOGIC IMMUNOLOGY

Marion B Sulzberger Rudolf L. Baer and Naomi M Kanof

Introduction

MANY OF the common technics described in Chapters 1 and 2 are used *in allergic conditions affecting the skin It is* therefore advisable that the physician read these chapters before referring to the measures particularly applicable in dermatology

HISTORY TAKING IN ALLERGIC DERMATOSES

History taking in dermatologic allergies follows the general lines set forth on page 6 The following particulars are intended for use mainly in *cases of allergic contact type eczematous dermatitis atopic dermatitis allergic forms of urticaria* and *allergic forms of drug eruptions* The taking of the history in allergic dermatoses resulting from infections infestations and insects is discussed under the particular disease entities

Just as in all other forms of allergy an accurate and complete history is likely to be *far more valuable than any other investigative procedure* And a detailed and directed history is *imperative in the selection of allergens for skin testing* Frequently a well taken his-

TABLE 15 —DERMATOLOGIC ENTITIES SKIN TESTS AND IMMUNOLOGIC PROCEDURES IN PROPHYLAXIS AND THERAPY

CLINICAL ENTITY	DIAGNOSTIC TEST		PROPHYLAXIS		SPECIFIC THERAPY	
	Typ	al	Type	V l	Typ	V l
Acne vulgar s	No e		None		A o dance of con tr butory f tors—iodides bromides s lected foods such as chocol te nuts cheese fish hellfish	*Often of co sider able lue*
Acti omycos s	Act nomycin test i tracuta eous n ject on of 0 1 cc acti myc n re dat 48 72 h Response i *el vated pap l* and erythem	*Not est bl shed*	No e		None	
A hrax	No e		None		Pass e immun za t n w th mmun serum i t e o sly	*Often f some al e n cases refr ctory to ther forms of t e tment*
Atop c dermatitis in older childre adolescents and ad lts (lichen chron icus s mplex d ssem atus d sseminated neurodermatitis flexural eczema d ther c pruritus etc)	1 Sc tch or i t cutaneous test w th suspected inh l d ngested or con tacted protein allergens read at 20–30 m n Response wheal and/or erythema	*1 Of q i nabl al ften f ls i nd cat the l cal s i i vity e s bita i n g i sk n s t it may be ca s s f exa erb t ons d s bst nc i l i g t ong pos t k n test re po i t may often be n-nocuous c nically*	1 A dance a d protect on *aga nst proved* nhal d i gest ed and co tacted causal alle g ns 2 Special pre-caut ons preced ng dm n stra t on of fore gn serums	*1 Of some value* *2 Of gr at alue*	1 Avoida ce d protect on again t proved nhal d i gested a d contact d c usal allerge s 2 Ch g f en ronment 3 Hypose tiza t on w th specific *e tracts*	*1 Of some alue* *2 Of g at v l e* *3 P a e t m thod f n lue*

TABLE 15 CONTINUED—DERMATOLOGIC ENTITIES SKIN TESTS AND IMMUNOLOGIC PROCEDURES IN PROPHYLAXIS AND THERAPY

CLINICAL ENTITY	DIAGNOSTIC TEST		PROPHYLAXIS		SPECIFIC THERAPY	
	Typ	V l	Typ	V l	Typ	Val
A p c d m (t.)	2 A o da ce a d -exposu e te ts	Of som val e b s lable t t fo find ng i c i g g ts				
Bl stomyco s (North Am can)	Blastomyc n test racuta eo s n-ject on of 0 1 c bl o yc n read t 48 72 hr Re-po se nfiltrated pap le a d ryth em	Of s m al e pos t e r ct on d cas s b gh p b b l ty of pr s o past nf t n but neg t espon e do n t xclud blast my s	None		Spec fic hyposens t zat o w th blas-tomyc racuta eo ly	Perh p of s m alue as add t al t eatm nt f ther form of t e tment g nt t f to y response
Chanc d	l o-Ree erma t t cu eous n ject f 0 1 cc D c ey v ead t 48 72 hr Respo s erythema nfiltrated p pul d pust le	Of m al p t e a ct n nd cat pr s t p e ous fect (not n arly as pe-cifically diag stic as the Fres t st)	N n		N	
Co c d o d	Cocc dio d n t t racut eous t ect on of 0 1 c. coc d o d n read at 48–72 hr Respo se filtrated pap le and eryth ma	Of d st nct alue p s t ve re t n nd cat s pr e s pres us fection	None		Spec fic hypose s ts t n w h cocc d o d	P b ps of some al t add t o l t eatment f p se to other f rms f ther py t n at sfact y

TABLE 15 CONTINUED—DERMATOLOGIC ENTITIES SKIN TESTS AND IMMUNOLOGIC PROCEDURES IN PROPHYLAXIS AND THERAPY

CLINICAL ENTITY	DIAGNOSTIC TEST		PROPHYLAXIS		SPECIFIC THERAPY	
	Typ	V l e	Typ	V l	Typ	V l
F gous i fectio s (uperficial) of gl brous sk n (gworm t nea c rc n ta d ma ophyto t nea cruris jock itch a hlete s foot etc)	1 Tr hophyt n test for tubercul n type react on i tracutaneo s in ject on f 0 1 cc t chophyt read at 48 72 h Response fil t at d p pule a d e ythema T ch phyt test for t l re ct o ntracu ta eous j ct cf 0 02 c of t chophyti r d t 0–30 m n Response wheal d/or fl re	*I R ly of v l e t es many normal adults e a t to t chophyt n M st perio s u tb acts o f go td a e strongly h pre s s t e to lack of sp se te ds t rul ous fung s ed* *Of me v l e l is fy g l go s s f t s M y nd ind al fected u th T p p m gi e ub l react on Of t l a s erys pel s l ke ep dermophyt d*	No e		Hypo en t z tion w th t i h phytin	*Ge ally of no l f limit d al n som c ses f ery p las l ke epiderm phytid perh ps f some t In in occ l ses of ecz matous epiderm phyt d u h ch a e refra to y t ther forms of therapy*
Fu gu s nfect o s (c f h ty are s)	*Tr chophyt n test for tubercul type react on (see above)*	*R clv f val e f t s u th n thropoph l c f g cfs n f il to ea s f ct u th z oph l c f g ofs n po s e s nt*	No e		Subcut eo s inj ct ons of tr chophyt n	*M y be of v l s acc ler t g be l ng of s me c ses p r t ularly of f c ts s u th zoophil c fu gi*

TABLE 15 CONTINUED—DERMATOLOGIC ENTITILS SKIN TESTS AND IMMUNOLOGIC PROCEDURES IN PROPHYLAXIS AND THERAPY

CLINICAL ENTITY	DIAGNOSTIC TEST		PROPHYLAXIS		SPECIFIC THERAPY	
	Typ	V l	Typ	V l	Typ	V l
G n l ma n l e	T bercul test e cut neo s t ct o s f d l t f tubercul re d c 48 72 h Resp nfil d p p l and yth m	Of som al e n d ffer tial diag s s m s cas b a l s ergy t t b l	N		No e	
H pc mpl	None		1 V c ons with sm llpox cc e Vacci tio s w th he pes mplex bl er fl d	1 M y b of t ma al s e rre t as t 2 V al t t bl b d	N e	
H rpes zoste	None		N		N n	
Infa t le cz m of atop c type (i fa t l ec ema m lk cru t etc)	1 Sc tch t t cut e test w th spected haled gested cont ct d p o te all gens read at 20 30 m n Respo se whe l d erythem	1 Of q t bl l m t d l e oft n f als t s dr cate th l cal sen s ty s bst ces neg t on k n s t m y be es f e erb t ns bst es l t ng k t t re t s m y ft n b e o on l c l p s s	1 A o da ce a d pro ct g st p o ed t h l d inges d a d con t ct d lic t g ll rge s	1 Of c der ble al	1 Av dance and p otect on g t p ed i haled ing red a d tacted llcit g llerge s	1 Of c der bl tal

TABLE 15 CONTINUED—DERMATOLOGIC ENTITIES SKIN TESTS AND IMMUNOLOGIC PROCEDURES IN PROPHYLAXIS AND THERAPY

CLINICAL ENTITY	DIAGNOSTIC TEST		PROPHYLAXIS		SPECIFIC THERAPY	
	Type	*V l*	*Typ*	*V l*	*Typ*	*Val*
I fa tile eczema (cont.)	2 Avo d ce and re-exposure tests	*2 Of c ns der ble val e best available test for fi ding el s ng gent*	2 Special pre-cautio s preced ing adm n stra t on of fore g serums	*2 Of great alue*	2 Hyposen t za t on with spec fic extr cts	*2 Generally of no al e*
I sect bites	I trac taneous t st for 24–48 hr respo se	*M y be of some value in certain t bercul n-type papular forms of hypers ns tivity*	No e		Hypose iti at on with spec fic extracts	*Of cons der ble val in s me s ere art carial r ct ons perh ps of value n some ca s of t berc l n type r t on*
Lep o y	Leprom n leprolin a d lep in tests	*Value not e tab l sh d perh ps of some value n d fferentiat g be-tween progress ve forms nd forms with a tendency to resistanc L p o mat us forms ft n hypoergic t berc loid forms and those w th better p ognoses often hyperergic*	No		N	

TABLE 15 CONTINUED—DERMATOLOGIC ENTITIES SKIN TESTS AND IMMUNOLOGIC PROCEDURES IN PROPHYLAXIS AND THERAPY

CLINICAL ENTITY	DIAGNOSTIC TEST		PROPHYLAXIS		SPECIFIC THERAPY	
	Typ	V l	Typ	V l	Typ	V l
Lymph g s lo- ma ve ereum	F e test mod f c o trac eo injection of ant ge p pared f om pro ed hum c r from rus cultured ch ck embryo read s 48 72 hr R po rych ma, infil tr ted p p le pus l	*Of gr at l p s e e s usually indicat p ens o p o f s n*	No e		Act ve imm za tion w th human or ch ck mbryo ugen	*Of l m t d and q t on bl al e as dd t onal tr t m t f tp s to ther form f tr atment s sf ctory*
Mo l as s (o d myco s te d g cal blastomyc c ero on)	O d omyc n te t t acute co s n ject on of 0 1 cc d omyc re d at 48 72 h R po se eryth ma and fil ed p p l	*Of o pr t cal alue ex pt as c trol f tr b phyt t t*	No e		No	
S o do s (Boeck s sarcoid Da ier R sy s coid Schauma n s d s- ease n nsuppu rative tubercu los s [Pi ne] etc)	T bercul te t tracutaneous i ject on of d lutio s of tub rculin read t 48 72 hr Response infil trated pap l a d erythema	*Of m al d fferential diagn s s m s tat s ba a lat e ergy to t berc lin*	N		No e	

TABLE 15 CONTINUED—DERMATOLOGIC ENTITIES, SKIN TESTS AND IMMUNOLOGIC PROCEDURES IN PROPHYLAXIS AND THERAPY

CLINICAL ENTITY	DIAGNOSTIC TEST		PROPHYLAXIS		SPECIFIC THERAPY	
	Type	Value	Type	Value	Type	Value
Sporotrichosis	Sporotrichin test: intracutaneous injection of 0.1 cc. sporotrichin read at 48–72 hr. Response infiltrated papule and erythema	*Of value; positive reaction indicates present or previous infection*	None		Hyposensitization with sporotrichin	*Perhaps of some value as additional treatment if response to other forms of treatment is unsatisfactory*
Staphylodermas (furuncles, carbuncles, sweat	None		Hyposensitization with autogenous (or stock) vaccine and/or active immunization with toxoid	*Of value in some cases*	Hyposensitization with autogenous (or stock) vaccine and/or active immunization with toxoid	*Of limited value in some cases*
Streptodermas	None		None		None	
Syphilis	Luetin test: intracutaneous injection of 0.1 cc. luetin read at 48–72 hr. Response infiltrated papule and erythema	*Of questionable or limited value in late secondary and in tertiary syphilis; not very specific*	None		None	

TABLE 15 CONTINUED—DERMATOLOGIC ENTITIES SKIN TESTS AND IMMUNOLOGIC PROCEDURES IN PROPHYLAXIS AND THERAPY

CLINICAL ENTITY	DIAGNOSTIC TEST		PROPHYLAXIS		SPECIFIC THERAPY	
	Typ	V l	Typ	V l	Typ	V l
T berculode m	T bercul te t i acut eous jection of q titat dil ti s of tube cul n read at 48 72 hr Respo se nfil trated pap le d rythem	Of m al d ffer ntial diag o- si of sub l derm r n t OTK 1 5 000 s normal n c t s pers ns er 21 25 y R a t t OTK 1 1 000 000 t 1 100 000 d t hyper e ty d gg t l p t lgar s t b lo s s colliq t err cot th hyperatg t berc l derm H u er a s g f t mber f per o u b t h c lsds (p p l t eryth m s d t m) ar le s s s t e th r- m l nd d s t nt l s 1 of OTK 1 1 000 o 1 100 r gr s are je t d	None		Hypose s izat o by repeated intra cu eous jections of t bercul in as e d g c ce tions	Of ery l ttle or no alue except perh ps isolated nstanc t f t ber loderms

TABLE 15 CONTINUED—DERMATOLOGIC ENTITIES SKIN TESTS AND IMMUNOLOGIC PROCEDURES IN PROPHYLAXIS AND THERAPY

CLINICAL ENTITY	DIAGNOSTIC TEST		PROPHYLAXIS		SPECIFIC THERAPY	
	Typ	V l	Typ	V l	Typ	V l
Urticar a (llergic) (hives g o eurot c edema, etc.)	1 Scratch or intracut neou t w th suspected n h led i gested o tacted all ge s r ad t 20 30 m n R sponse wh al a d/ r fl e In dd t on test wi h phys c l agents (h t cold l ght)	*1 Sl ght ps u th phy al ge t ft f ls se s t ty s b st gat s n t d cat cl n c l k n test m y x erbate d s b tan l i g p t k re spo es n y fr b s ous l ally*	A oid nce d protect o again t h led i g t d and onta ted alle g ns	*G ner lly of alu*	1 A o d ce and p ote tio g st inhal d g sted d co tacted allerg ns	*1 G ner lly f g e s v l e*
	2 A dance and re-expo u est	*2 Of gr at al e best al bl t t fo fi d g ca r re-exp s re ts tom t m d ger*			2 Hyposens t a tio w th spec fic ex acts	*2 Ge erally of no al e*
Verruca vulgaris	Non		No		Act e immun tion wi h wart v cc ne	*Val e not yet est bl shed*

tory either makes skin tests unnecessary or reduces to a practical mini mum the number of allergens which must be applied in skin tests

PERSONAL HISTORY—The physician s questions must first be directed toward those allergens which are notorious for producing the particular type of allergic dermatosis under consideration All questioning should be designed to discover chronologic relation ships between exposure to allergens and the onsets exacerbations or recurrences of the dermatosis and between the reduction or cessation of allergenic exposures and the improvements or remissions in the dermatosis

Since histories of onset and evolution of allergic dermatoses vary widely history taking must be individualized No catch all list of questions can be provided However the following suggestions will perhaps indicate the general form of approach which can be adapted to suit the individual case

1 When did the eruption begin?

2 At what site(s) did it begin?

3 Was the onset sudden or gradual?

4 When did the eruption begin to spread?

5 What was the direction and course of the spread?

6 Has the eruption continued or grown constantly worse since its onset? Or have there been remissions and exacerbations?

7 If there were remissions exactly when did these occur? With what events or exposures can you connect the exacerbations? The remissions?

8 Has the eruption disappeared completely at any time(s) since its onset? If so under what circumstances? And for how long did the skin remain well?

9 Do recurrences always start in the same site(s)?

10 Is the eruption worse at any particular time of the day week or year? In any particular dwelling? Work place? Or in any other en vironment?

11 Have you noticed whether the eruption regularly improves or gets worse during weekends? During vacations? After a change in your type of work? Or on a business trip? On any other trip or sojourn? Or under any other change in your environment or activities?

12 Have you moved to a different place of residence? Have you changed your place or type of work? If so when?

13 Have any changes been made in your home? Any new furniture or equipment?

14 Have you had any other illness? (Include minor ailments) Have you taken or received any medicines? Have you been to a doctor or dentist? If so what did he do and prescribe? Have you taken *anything* for headaches? Sleeplessness? Indigestion? Stomach ache ? Constipation? Sinus trouble? Eye trouble? Nose trouble? Ear trouble? Colds? Menstrual pain? Etc

15 Have you used any external medicaments? Any eye drops? Nose drops or sprays? Suppositories? Bandages? Contraceptive preparations? Venereal disease or other prophylactics? Have you had any beauty treatments? Massages? Special medicated baths? Hair dressing procedures?

16 Have you eaten any unusual foods recently? If so what occurred?

17 Have you noticed anything that makes your rash worse? Any food? Any drinks? Any medicine? Any clothing? Any activity? Any illnesses? Menstrual state?

18 What sort of treatment have you used for *this eruption?* At the beginning? Later on? Did any form of the treatment appear to irritate your skin? Or make your condition worse? Or better? Or better at first and worse later on?

19 Have you, or anybody who is living with you bought or been given anything new during the days or weeks before the onset of your trouble? Clothing? Cosmetics? Household articles? Plants? Externally used or inhaled or sprayed drugs?

20 Have you previously had any skin trouble which resembled your present trouble? If so when did it start? How long did it last?

21 Did you find out or do you suspect the cause of your previous trouble? Was the cause proved by test? By other means?

22 Is there anyone who lives or works with you or who participates in the same sports games hobbies who has skin trouble similar to yours? Or any other skin trouble?

The following is a list of some of the principal activities and exposures which should be investigated when taking the history in a case of allergic dermatosis of unknown etiology

1 Washing and cleansing materials used for personal hygiene

2 Cosmetics (also cosmetics used by other members of the family)

3 Medicaments (often important in urticarial and atopic conditions and of course in all drug eruptions)

a) Taken internally (including rectal vaginal or nasal route etc)

b) Administered parenterally (injected inhaled etc)

c) Applied externally (to self and/or to others)

4 Materials worn during the day

a) At home

b) At work

c) Going out

d) On special occasions trips sports etc.

5 Materials worn at night

a) In bed

b) For lounging

6 Materials encountered in own home

a) Furniture and furniture covering stuffing bedding and bedding materials (particularly important in urticarial and atopic diseases)

b) Carpets drapes etc

c) Waxes paints lacquers polishes cleansing solutions etc

d) Sprays for clothes furniture carpets plants against insects moths etc

e) Domestic animals and materials used for their cleanliness and in maintenance (particularly important in urticarial and atopic conditions)

f) Clothing cosmetics internal and external medicaments used by other members of the household

g) Plants and flowers sprays fertilizers and other materials used in their maintenance (particularly important in urticarial and atopic conditions)

7 Materials encountered on way to and from work

a) In the conveyance (car steering wheel driving gloves etc)

b) From fellow passengers

8 Materials encountered at work
  a) During and characteristic of the particular occupation
  b) Cleansers (soaps solvents other detergents)
  c) Protective materials used (clothing creams etc)
  d) Used in work done nearby
  e) Particles in the air dust, gases (particularly important in urticarial and atopic conditions)
  f) Encountered at places of eating recreation restrooms etc
  g) Encountered in other departments in which only occasional short periods of time are spent

9 *Materials encountered while traveling*
  a) In the conveyance
  b) In the hotel (consider all possibilities listed for questioning in own home)
  c) Fellow passengers (see 12)
  d) At places visited for business or amusement etc

10 Materials encountered while shopping
  a) Tried on
  b) Handled
  c) Carried
  d) Particles in the air dusts vapors (particularly important in urticarial and atopic conditions)
  e) Receptacles and containers used for packaging and carrying

11 Materials encountered during recreation
  a) In theaters movies restaurants etc (sprays etc)
  b) In places of worship
  c) In sports (participant and spectator)
  d) Gardening farming (particularly important in urticarial and atopic conditions)
  e) Bathing, swimming, beach sun (oils sun tan preparations)
  f) Reading
  g) Photography stamp collecting, carpentering etc.
  h) Musical instruments
  i) Games
  j) Visits to friends

12 All allergenic materials used or worn or carried by other persons (family or friends or persons encountered at work or at other places)

This general outline is supplemented by the particulars of history taking given in the sections on the individual allergic dermatoses

FAMILY HISTORY —That distinct hereditary tendency which exists in many cases of respiratory atopy—e g hay fever and allergic asthma—is generally found only in the atopic dermatoses In about 50 per cent of patients with atopic dermatoses there is a *family* history of infantile eczema atopic dermatitis hives angioneurotic edema asthma hay fever or vasomotor rhinitis But in the other common allergic dermatoses such as allergic drug eruptions and allergic eczematous contact type dermatitis in fact in virtually all allergic cutaneous diseases other than atopic dermatitis there is usually *no distinct familial tendency either to similar eruptions or to other allergies*

HISTORY OF ASSOCIATED CONDITIONS —In many cases of allergic dermatoses there is an *individual predisposition* to a particular form of allergic response Associated conditions may therefore provide clues to the type of allergic dermatosis from which the patient suffers

Adults and adolescents who have atopic dermatitis not infrequently have had previous attacks of infantile eczema prurigo or childhood flexural eruptions in addition, they often give a history of present or previous attacks of asthma or hay fever

Patients with allergic contact type eczematous dermatitis not infrequently have had previous attacks of the same type of dermatosis These may have been due either to the same allergen or to some other allergen and may have been clinically similar to the present attack or may have presented a different clinical picture and/or involved different localizations

Patients with allergic urticaria or angioneurotic edema not infrequently have had previous attacks of urticaria or angioneurotic edema from the same allergen or from an unrelated allergen.

Patients with allergic drug eruptions not infrequently have had pre vious attacks of drug eruptions from the same or some other drug and usually (but not always) of the same morphologic type as the present eruption.

Sex—There is *no* evident sex bound predisposition toward any particular form of cutaneous allergy However certain allergens are likely to be encountered preponderantly by the male or by the female

Women are more often exposed to cosmetics hairpins hair lacquers furs jewelry antiperspirants depilatories menstrual napkins household cleansers and other household articles etc Men are more often exposed to suspensories shaving materials after shaving lotions, hair tonics certain articles of sports or work, leather hat bands etc

Race—There is no evident racial predisposition to any particular forms of cutaneous allergy It appears likely however that suscep tibility to *eczematous contact type sensitization is somewhat less among Negroes than among whites* Certain apparently racial differences are explicable by the fact that certain allergens are more likely to be encountered by one race than by others

Negroes are more likely to be exposed to bleaching creams chemicals for hair straightening etc whereas white persons are more likely to be exposed to sun tan and sun protective lotions and creams

Geographic Location and Season—Allergens may sometimes be suspected or ruled out on the basis of geographic location or of season Thus ragweed pollen must be suspected as an inhalant and as a contact allergen in many localities from about July 15 to September 15 but can often be ruled out as a possible eliciting agent for allergic dermatoses in other seasons or in other localities Similarly poison ivy chrysanthemums and numerous other plants have places and seasons for maximal exposure

Occupation and Hobbies—The search for possible eliciting allergens must always include exposures encountered in the patient s work recreation and hobbies Certain activities are known to present particular hazards of exposure to notorious contact type

inhalant or other atopic allergens Under these circumstances it is advisable *first* to consider the most notorious allergens in the particular activity However it must be remembered that even usually innocent materials with a low sensitizing potential can occasionally be the cause of allergic reactions

The periodicity of remissions and exacerbations or recurrences frequently directs suspicion to allergens encountered in particular activities

INTERVAL BETWEEN EXPOSURE AND APPEARANCE OF ERUPTION —It is necessary to recognize the following three chronologic periods which are almost universally encountered in immunologic reactions Their recognition is often of decisive importance in evaluating the significance of the time interval between exposure to the suspected allergen and the first appearance of the reaction

1 *Period of 'Immunity or Refractoriness to Sensitization*— In many cases there is no demonstrable period of immunity to sensitization the *process of sensitization starts at once immediately on the first exposure to the allergen* In other cases the period of immunity to sensitization is *indefinitely long* sensitization *never* develops despite more or less prolonged and/or repeated exposure to the allergen

In still other cases the period of immunity to sensitization varies from days to weeks months or years i e it is only *after a certain (but individually variable) period of exposure* that the patient *begins* to develop a sensitization Thus after a period of weeks months or years the patient develops an eruption on exposure to an allergen which he tolerated without manifest reaction during all previous exposures

2 *Incubation Period of Sensitization* —The sensitization process once it has begun to develop usually takes a certain period of time generally five days to three weeks to reach that level which *can result in clinical manifestations* This period of development is the *incubation period* The occurrence of clinical manifestations at

the end of the incubation period will of course depend on the presence of enough allergen to elicit a reaction in the newly sensitized tissue

a) The allergen can be available in the form of *residual* allergen remaining from the original exposure(s) This occurs in serum sickness in most infectious processes and in those eczematous and other sensitizations in which *spontaneous flare ups* at the sites of previous exposure occur at the end of several days to weeks The *practical importance* of this concept is evident when *an allergic condition appears spontaneously* days to weeks after the last exposure to the causal allergen

b) At the end of the incubation period the residual antigen re maining from the first exposure is insufficient to produce a clinical reaction The clinical reaction appears only when there is a re exposure i e when additional newly introduced allergen is en countered by the previously sensitized tissues *This is the more* common mechanism of reaction

3 *Reaction Time of Sensitivity*—Even after the end of the incubation period or the full development of sensitivity when the already sensitized skin is exposed to the allergen in adequate amounts there is an interval of seconds minutes hours or days between exposure of sensitive tissue to its allergen and the development of a manifest reaction This may be termed the *reaction time* The length of the reaction time varies characteristically in the dif ferent forms of cutaneous allergy It may also vary from patient to patient and sometimes even with the quantity of allergenic exposure The average reaction time for urticarial responses is seconds to minutes for eczematous and tuberculin type responses it is hours to days

The practical bearing which these three immunologic phenomena have on history taking may be summarized as follows

1 When taking the history to discover possible eliciting agents the physician must consider not only *new* agents to which the patient has been but recently exposed but also agents to which he has

previously been exposed with impunity for weeks months or years (during his period of refractoriness to sensitization)

2 When trying to discover eliciting agents the physician must recall that the last obvious allergenic exposure may have taken place either (*a*) several days to weeks *before* the first clinical manifestation (the interval between eliciting exposure and appearance of the presenting eruption consisting of the incubation period *plus* the reaction time) or (*b*) only seconds minutes or hours before the first clinical manifestation (because the sensitivity was already fully developed usually owing to previous sensitizing exposure and the interval between allergenic exposure and manifestation consists only of the reaction time)

SKIN TESTS AND OTHER IMMUNOLOGIC PROCEDURES IN DIFFERENTIAL DIAGNOSIS OF CERTAIN ECZEMATOUS AND ECZEMATOID ERUPTIONS

The differential diagnosis between eczematous allergic contact type dermatitis atopic dermatoses and other eczematous and eczematoid eruptions can usually be established on clinical and other evidence without recourse to immunologic measures But in the atypical transitional or combined forms clinical differentiation is often difficult and in such cases skin tests and other immunologic data may be helpful in making the diagnosis

Table 16 shows that, on the basis of statistical probability immunologic data can be of some weight in differential diagnosis Thus the presence or absence of eczematous responses to routine patch tests and of wheal responses to routine scratch or intracutaneous tests can be evaluated on a statistical basis The usefulness of such tests for differential diagnosis is founded on the following facts (1) *A patient presenting a contact type allergic eczematous dermatitis elicited by any one substance is on the whole more likely to react to patch tests with a series of common eczematogenic allergens than is a patient with any other form of dermatosis* Several positive reactions thus speak somewhat in favor of contact type

TABLE 16—IMMUNOLOGIC DATA IN DIFFERENTIAL DIAGNOSIS OF CERTAIN ECZEMATOUS AND ECZEMATOID ERUPTIONS

	Contact-Type Allergic Eczematous Dermatitis	Atopic Dermatitis	Seborrheic Dermatitis	Other Eczematous and Eczematoid Eruptions
Age of onset	Any age; not usually preceded by infantile eczema; more common in adults	Often appears in three phases: (1) infantile eczema; (2) childhood form 6–10 yr; (3) adolescent and adult form 13–30 yr	Perhaps sometimes preceded by seborrheic type of infantile eczema(?); late childhood, early adolescence or any time thereafter	Not usually preceded by infantile eczema
Family and personal history of atopic diseases (hay fever, asthma, infantile eczema)	Negative, i.e., of normal incidence	Positive, i.e., of abnormally high incidence in both family and personal history	Negative, i.e., of normal incidence	Negative, i.e., of normal incidence
Character of allergens	Water- or oil-soluble simple compounds (nonproteins), e.g., dyes, medicaments, etc., products of plants (in oily fraction), synthetic chemicals, etc.	Ingested or inhaled substances, commonly either protein in nature or associated with proteins (may be elicited by external contact, probably through transepidermal penetration)	No known allergic basis	In most entities no *known allergens*
Free antibodies	None conclusively demonstrated	Prausnitz-Kustner passive transfer antibodies common	No	*None*
Eosinophilia	Negative, i.e., of normal incidence	Positive, i.e., of abnormally high incidence	Negative, i.e., of normal incidence	Negative, i.e., of normal incidence

Based on table in Sulzberger, M. B.: *Dermatologic Allergy* (Springfield, Ill.: Charles C Thomas, Publisher, 1940).
Combinations of any two or more forms occur. The combined forms present the combined characteristics of the forms concerned.

TABLE 16—CONTINUED

		Contact Type Allergic Eczematous Dermatitis	Atopic Dermatitis	Seborrheic Dermatitis	Other Eczematous and Eczematoid Eruptions
Results of Skin Tests	Immediate wheal reactions to scratch or intracutaneous tests	Generally negative to series of common urticario-genic allergens, i.e. of normal incidence	Generally positive to some members of a series of common urticariogenic allergens, i.e. of abnormally high incidence	Generally negative to a series of common urticariogenic allergens, i.e. of normal incidence	Generally negative to a series of common urticariogenic allergens, i.e. of normal incidence
	Eczematous reactions at 24-48 hrs. to patch tests	Generally positive to some members of a series of common eczematogenic allergens, i.e. of abnormally high incidence	Generally negative to a series of common eczematogenic allergens, i.e. of normal or perhaps even subnormal incidence	No adequate series has yet been investigated with patch tests†	Generally negative to a series of common eczematogenic allergens, i.e. of normal incidence
Significance of specific *hypersensitivity* to allergens		Very important	Apparently important but in many cases *not of demonstrable clinical significance*	No hypersensitivity to any known allergens has been demonstrated to be of clinical importance	In most entities, no hypersensitivity to *any known allergens* has been demonstrated to be of clinical importance

† Studies of Rostenberg and Sulzberger suggest a higher than normal incidence of reactions to patch tests

allergy (2) *A patient presenting an atopic dermatitis is on the whole more likely to react to scratch tests with a series of common wheal-producing allergens than is a patient with any form of non-atopic eczematous or eczematoid dermatosis* Several positive reactions here thus speak somewhat in favor of atopic allergy

When considered alone these immunologic data are of course of as *little differential diagnostic value* as the isolated results of most other clinical or laboratory test procedures However in conjunction with the history and with clinical findings as well as with the other pertinent observations the additional evidence furnished by immunologic data may aid in differential diagnosis

Acne Varioliformis (Acne Necroticans)

PROPHYLAXIS AND TREATMENT

This disease is of unknown etiology It is not established that staphylococci are the principal causal agents However immunization with staphylococcus toxoid or combined hyposensitization with vaccine and immunization with toxoid may sometimes be of value In our experience some chronic and severe cases may be materially benefited by these procedures

Of course the immunologic methods are secondary to the usually effective local and general treatment, including the avoidance of foods and drugs as described in the section on dermatitis herpetiformis For materials and method of treatment, contraindications and dangers see pages 364 f

DIAGNOSIS

No immunologic method available

Acne Vulgaris (Cystic Acne Chin Acne of Older Women)

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

No immunologic method available

TREATMENT

1 Elimination of certain foods is frequently of great value Chief among these foods are chocolate in all forms and guises nuts (including peanuts) sharp cheeses shellfish and fish pork and pork products *It is not known whether or not the action of these foods which frequently make acne vulgaris worse is based on an immunologic form of hypersensitivity*

2 Hyposensitization with autogenous staphylococcus vaccine and active immunization with staphylococcus toxoid are generally of no value in ordinary juvenile acne However these measures may be tried in severe cases of acne and particularly in cystic forms and in chin acne of older women when all conventional forms of therapy have failed For materials methods contraindications and dangers of treatment with staphylococcus vaccine and/or toxoid see pages 364 f

Actinomycosis

INCUBATION PERIOD

Probably a few days to weeks

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

SKIN TESTS —*Indication* —The differential diagnostic value of skin tests with *actinomycin* is not established The method of testing is the same as that with tuberculin trichophytin etc

Material —Actinomycin is prepared from cultures of Actinomyces bovis It is not commercially available

TREATMENT

The value of immunologic therapy with actinomycin is not yet established The materials for treatment are not commercially available

Anthrax

INCUBATION PERIOD

Usually two to three days but in maximal instances up to eight days

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

No immunologic method available

TREATMENT

PASSIVE IMMUNIZATION —*Indications*—Antianthrax serum therapy is generally indicated only for those patients with anthrax who have not responded to or who are intolerant to sulfonamide therapy The apparent effectiveness of the new drugs and antibiotics has reduced the indications for immunotherapy

Materials—Antianthrax serum is commercially available from

Lederle Laboratories Inc 50 cc vial

Parke Davis & Co 50 cc syringe container with needle and gravity tube

Sharp & Dohme Inc *Antianthrax Serum (Mulford)* 50 cc double end vial with outfit for intravenous use

Method—Doses of 200–500 cc are given intravenously and repeated every 12–24 hours until edema surrounding the anthrax lesion is controlled

Contraindications and Dangers—The usual dangers of serum reactions are present and the usual precautions must be observed

TRANSFUSION OF WHOLE BLOOD FROM IMMUNE HUMAN DONOR—*Indication*—This is said to be of some value in severe cases of anthrax which have not responded to sulfonamide and antianthrax horse serum therapy

Material and Method—Transfusion of 500 cc whole blood from an individual who has had an infection with anthrax is given and if necessary may be repeated after a few days

Contraindications and Dangers—The usual precautions against transfusion reactions must be observed

IMMUNITY

It is not known whether immunity is acquired after an attack of the disease However cases of recurrent anthrax infection are said to be rare

Atopic Dermatoses

INFANTILE ECZEMA (ATOPIC DERMATITIS OF INFANTS) DISSEMINATED NEURODERMATITIS PRURIGO ETC (ATOPIC DERMATITIS OF CHILDREN ADOLESCENTS AND ADULTS)

The skin diseases associated with *atopy* (i.e with that form of human allergy which evidences a familial tendency to hay fever allergic asthma and certain other forms of allergies and to *certain characteristic dermatoses)* are here designated as the *atopic dermatoses* These form one of the largest groups of skin troubles and one of the most difficult to manage

The *infantile form* of atopic dermatoses (atopic dermatitis in infants) usually occurs between the first month and the second year of life and presents the clinical picture quite generally called *infantile eczema* The *childhood* forms of atopic dermatoses usually occur between the second and the tenth or twelfth year The *adolescent* and *adult* forms generally occur at the early onset of puberty and usually clear before the third decade The childhood adolescent and adult atopic eruptions are variously known as disseminated neurodermatitis prurigo pruritus with lichenification lichenified dermatitis chronic flexural eczema or dermatitis or—most unfortunately and confusingly—just chronic eczema or "eczema

In all these forms the clinical role of allergens can on occasion be demonstrated However there is no satisfactory evidence that all cases of atopic dermatosis are entirely or principally due to

allergenic exposures On the contrary in many clinically typical cases no immunologic mechanisms are apparent and in many other cases even though there is evidence of specific hypersensitivity the allergenic exposures cannot be demonstrated to be the sole or even the major causes of the cutaneous troubles

The situation in an unselected group of atopic dermatoses is thus in many ways like that in an unselected group of chronic bronchial asthmas Just as in asthma, only about 50 per cent of the patients with atopic dermatitis give wheal reactions to skin tests with common food and environmental allergens and, similarly it is not unusual to find that the food or other allergen which elicited the skin test reaction cannot be shown to be of great clinical significance

In most cases of atopic dermatoses therefore systemic manage ment and nonspecific measures (including protection against direct skin irritants reduction of tensions and maladjustments through psychotherapy etc) and *above all* proper and individually adjusted *local* treatment often play the major part in bringing relief Never theless in many instances the harmful effects of specific allergenic exposures have decisive significance and immunologic approaches and the avoidance of possible causal allergens must not be neglected in any severe or long standing case

The following are among the immunologic measures of impor tance in atopic dermatoses

PROPHYLAXIS

1 The accepted measures for the *avoidance or reduction of ex posures* to the ingested inhaled or contacted allergens *are the only effective forms of prophylaxis* Hyposensitization with specific ex tracts effective in other forms of atopy (e g in many cases of hay fever and in some cases of allergic asthma) is generally of *no value* in atopic dermatitis

2 In all atopic persons the *utmost caution* must be observed in the *administration of foreign serums* In these individuals there is considerably more than the usual danger of severe or even fatal serum reactions

5 *Genetic prophylaxis* may be indicated in exceptional an selected cases The physician may find it desirable to warn marriag partners who suffer from severe atopic diseases and in whose fami there is a definite incidence of atopic diseases that their offsprin may be particularly susceptible to diseases of this group

DIAGNOSIS

SCRATCH OR INTRACUTANEOUS TESTS FOR DISCOVERING ELI ITING AGENTS —Scratch tests and intracutaneous tests are *genera ly of very limited value* in the discovery of eliciting agents in atop dermatoses In many individuals with atopic dermatoses skin tes will produce wheal reactions with allergens which can be show to be of little or no clinical importance In other words avoidan of the allergen which produced a positive reaction to a skin test wi often fail to produce improvement or remission and re exposu of the patient to the allergen will often fail to produce an exacerb tion or recurrence of the skin trouble Conversely allergens proved clinical importance in that they have been shown to produ exacerbations of the dermatosis may fail to elicit wheal reactio on skin test Despite these contradictions when other diagnost and therapeutic measures have failed skin tests may be of son help in suggesting possible eliciting agents

Materials —The choice of materials for skin testing for eliciting ager in atopic dermatoses can be based on routine series which inclu those allergens *recognized as the most common eliciting agents* of atop dermatoses at different ages Routine series for scratch testing in old children, adolescents and adults are listed on pages 211 and 219

The following is a short list of foods especially selected for routi scratch testing in infants and young children

Casein	Oats
Egg white	Orange
Egg yolk	Rye
Milk	Wheat

To these routine lists there should be added allergenic materials whi are selected according to circumstances applicable in the particular ca

This selection is based largely on the individual history and on observations of the course of the eruption The suggested line of questioning is given on page 249 It must be stressed once more that no rigid scheme will be found adequate and that the physician must fit his questions to the case In particular he must follow the clues suggested by the sequences of exacerbations and remissions and direct his interrogations toward so called protein allergens inhaled ingested or contacted in relation to the flare ups

For selection of test materials guided by the course of the eruption and the results of avoidance and re exposure to suspected agents the effects of avoidance and re exposure to suspected allergens are used In other words the results of dietary measures (p 59) and of avoidance and exposure to inhalant and environmental allergens (p 58) are compared with the wheal reactions to skin tests with these allergens

The selection of test materials according to localization of the eruption is of value in some cases Atopic dermatitis almost always affects characteristic areas (in *infants* principally the scalp and face in children adolescents and adults principally the cubital and popliteal spaces the neck and upper chest dorsa of hands) and these sites as a rule do not serve as clues for ascertaining eliciting agents However occasionally the sites of origin or of maximal development of the eruption direct attention to allergens which may be producing reactions through external exposure Owing to *transepidermal* penetration of the allergen the areas which *receive the direct and maximal external exposures often become sites of principal involvement* (e g legs from silk stockings chest and back from woolen sweater or silk dress or blouse hands from touching and preparing allergenic foods etc)

Application of Tests—Many of the materials for scratch testing and some of those for intracutaneous testing can be obtained commercially (pp 212 and 227) Materials which are not commercially available must be prepared in such manner concentrations and vehicles as to exclude the primary urticariogenic effects as well as other damage either local or systemic Directions for preparations and technic of use of test materials and the precautions to be taken are given in Chapter 1

Readings and Evaluation of Reaction—Readings are made at 10–30 minutes The results are evaluated as described on page 34

1 The immunologic or specific approaches to atopic dermatoses are in general secondary to the *nonimmunologic* methods of diagnosis external treatment and general management

2 The positive or negative results of skin tests in atopic dermatoses are of diagnostic and etiologic significance only when corroborated by

a) The clinical findings

b) The course (if results of avoidance and of re exposure are in disagreement with results of skin tests the evidence furnished by the former is conclusive)

c) The exclusion of other causes

Contraindications and Dangers—We have stated that we believe the nonspecialist may prefer to avoid the intracutaneous test methods and to confine himself to the use of scratch tests Scratch tests generally constitute a safe means of skin testing in the atopic dermatoses Nevertheless certain contraindications and dangers exist like all skin tests scratch tests should never be applied in a case of atopic dermatitis without proper knowledge and adequate indications

The observation of the precautions suggested on page 35 and of the following don ts will reduce the risks and errors

1 Don t test uselessly indiscriminately or in a haphazard manner

2 Don t test with those allergens which clinical evidence has shown capable of causing constitutional reactions severe asthmatic attacks etc in the particular patient Always remember that the patient with an atopic dermatosis may have not only a skin condi

tion but also visceral shock tissues which may react in a serious or dangerous manner

3 *Don t neglect treatment of the patient's skin* during the plan ning and execution of the skin tests and the evaluation of their results The skin lesions should be treated at once and for as *long* as necessary with the correct general and local measures—including x rays if indicated

4 Don t wait until a full blown severe constitutional or other reaction has occurred At the first signs of untoward local or general reaction institute the preventive or therapeutic measures outlined on page 92

TESTS BY REDUCTION OF EXPOSURE AND RE EXPOSURE TO ALLERGENS —These tests are of considerable value in many cases of atopic dermatoses but are often exceedingly difficult to perform They are most valuable in infants and young children and less so in older children adolescents and adults

This may be because patients in the older age groups show a greater tendency to multiple sensitizations and also because in older persons the more complex life and duties render more difficult the recognition and avoidance of potential offenders

The allergens for avoidance and re-exposure tests are selected in about the same manner as the allergens for skin testing viz (1) on the basis of the history and clinical course i e on the chron ologic relationships between certain allergenic exposures and the onset or exacerbation of the dermatosis and conversely on the reduction of certain allergenic exposures and improvement of the dermatosis (2) on the basis of general experience in cases of atopic dermatitis in infants older children adolescents and adults—an experience which indicates that *particular materials are notorious as eliciting agents in the different age groups*

In *infants* it is the rule that one or a few sensitivities are major factors in eliciting the clinical exacerbations Both food and inhalant allergens merit attention The most common eliciting agents among

these are cow s milk wheat or other cereals eggs citrus fruits spinach peas tomatoes fish fish products (including fish liver oils), house dust, substances coming from pillows mattresses bed ding rugs and drapes clothing materials (wool silk) In *older children adolescents and adults* multiple sensitivities to foods and inhalant allergens are the rule In general contrasted with infants foods have begun to lose some of their clinical importance as eliciting agents

Perhaps because of the practical difficulties we have found avoid ance and re exposure tests with individual allergens to be of little value in most cases of atopic dermatoses in adults However in the entire group of atopic dermatoses a general *avoidance of the com mon food allergens plus environmental control* i e the reduction of exposures to all common inhalant allergens may demonstrate whether or not multiple sensitivities are a major factor in producing the eruption

Avoidance of any particular allergen or group of allergens should be carried out for at least one week preferably longer Provided the skin condition is not being irritated by damaging external factors or by ill advised local therapy most patients show some degree of improvement within a few days following the avoidance of an allergen of clinical importance Re exposure to an allergen which is of clinical importance usually leads to an exacerbation or recur rence within a few minutes to one or two days For the technic of avoidance and re exposure tests with inhalant allergens (including environmental control) see page 71

TREATMENT

With the exception of elimination or reduction of exposure to eliciting agents no *immunologic* method is of general value [1] *Hypo sensitization with specific extracts is to all practical purposes ineffec*

[1] Proper topical therapy is by far the most effective s ngle form of treatment in most cases of atopic dermatoses The new antihistaminic drugs Pyribenzamine and Benadryl have in our experience been of value only in an occasional case of atopic dermatitis and have generally proved of little help in the management of most chronic and severe cases

tive in the treatment of atopic dermatoses Indeed we have gained the impression that the very hyposensitizing measures which are often so effective in respiratory allergies may make the skin condition worse rather than better

1 Elimination or reduction of exposure to selected *food allergens* may be of considerable value in the treatment of certain cases of atopic dermatoses in infants and young children It is the exception to find this procedure of great value in atopic dermatoses in older children in adolescents or in adults

2 Elimination or reduction of exposure to *inhalant and contact protein allergens* may be of some value in certain cases of atopic dermatitis of all age groups

Methods—The food and inhalant and contact allergens are eliminated according to the directions given on pages 69 and 75 Once the offending allergens have been found their avoidance must usually be continued for several years

Since atopic dermatoses are frequently outgrown exposure to small amounts of the offending allergens should be tried periodically, after several months or years of avoidance

IMMUNITY

There is no evidence that hyposensitization or acquired specific immunity of the skin can be produced with any degree of regularity in atopic dermatoses either through natural exposures or through deliberate hyposensitizing measures However *with time* temporary or permanent *hypo or desensitization appears to occur* in many cases Experience has shown that atopic dermatoses *tend to clear during certain periods of life*

Typical infantile eczema almost always disappears before age 2 atopic dermatoses in older children frequently clear up at the age of 9 or before and atopic dermatoses in adolescents and adults usually abate sometime between 18 and 25 Atopic skin eruptions are not unknown but certainly are rare after age 30 and the large majority of affected individuals remain free from recurrences after this age

The spontaneous remissions are among the facts which make the prospects for discovering hyposensitizing measures seem hope ful But as mentioned at the outset at present the best available *methods are local and systemic treatment plus the reduction of exposures to suspected allergens* Perhaps the one best therapeutic measure for atopic dermatosis of all age groups is a *radical change of environment* Like asthmatics patients with atopic dermatoses generally fare best in arid and desert climates Whenever feasible it is worth while to have the patient try out one place after another until he finds the one which suits his case As a rule the patient can tell within a week whether his new environment is of benefit Relief from itching is often dramatic and can occur within several hours Sometimes patients stay well only as long as they remain in the new environment But sometimes the patient who has been cured by a long or short period in a new environment may return to his original environment without suffering a relapse

It is not yet known whether the very real and consistent benefits of environmental changes result from changes (reductions) in allergenic exposures and thus are to be considered *specific* immuno logic forms of therapy There is however evidence that both specific and nonspecific factors may be concerned in many cases which respond to this treatment

Blastomycosis (North American Blastomycosis Gilchrist s Disease)

INCUBATION PERIOD

Generally not ascertainable (probably days to weeks)

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

SKIN TEST —*Indication* —Skin test with *blastomycin* is generally of only limited differential diagnostic value

Material—Blastomycin is prepared from cultures of Blastomyces dermatitidis It is not commercially available

Method—Intracutaneous injection of 0 1 cc blastomycin is given in the flexor aspect of the forearm or arm The test is read at 24–48–72 hours

Description and Evaluation of Reaction—The reaction appears at 24–48 hours and usually persists for two to four or more days The response is indicated by an erythematous papule or an infiltration about 1–2 cm in diameter The center of the papule is pustular at times

A *positive* reaction indicates that the individual has been infected with B dermatitidis but does not necessarily signify that the presenting signs of disease are due to B dermatitidis infection Once established skin sensitivity probably lasts for life A *negative* reaction does not rule out infection with B dermatitidis for proved cases of blastomycosis with negative reactions to the blastomycin test have been observed

Contraindications and Dangers—Generally none

TREATMENT

Immunologic therapy is said to be of value in some cases Materials are not commercially available The procedure is analogous to that described for trichophytin It should be combined with chemotherapy

IMMUNITY

Blastomycin injections may perhaps increase the resistance in some cases We could find no information on the presence or absence of acquired resistance to reinfection

Chancroid (Soft Chancre, Ulcus Molle)

INCUBATION PERIOD

Usually three or more days (limits are a *few hours* to *four to five days*)

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

SKIN TEST—*Indication*—The skin test (Ito-Reenstierna test) with *Ducrey vaccine* (chancroid vaccine) is generally of value in differential diagnosis

Material—Ducrey vaccine is a suspension of killed Hemophilus ducreyi (streptobacillus of Ducrey) This vaccine is commercially available from

Lederle Laboratories Inc. 0 2 cc for 2 tests and 5 cc for 50 tests

Method—Intracutaneous injection of 0 1 cc Ducrey vaccine is usually given in the flexor aspect of the forearm or arm The test is read at 24–48–72 hours

Description and Evaluation of Reaction—The reaction appears at 24–48 hours and usually persists for two to four or more days The response is indicated by an erythematous and infiltrated reaction about 1–2 cm in diameter The center of the papule is pustular at times

A *positive* reaction indicates that the individual has been infected with H ducreyi. It does not necessarily signify that the presenting signs of disease are caused by chancroid infection since the skin sensitivity produced by infection lasts for years and perhaps for life (compare tuberculin trichophytin Frei test, etc) A *negative* reaction indicates that the patient has never been infected with chancroid bacilli, that he is in a state of refractoriness or anergy or that the infection has taken place such a short time before that the skin has not yet become sensitive to the test material If the last alternative is suspected a later repetition of the test is indicated.

Contraindications and Dangers—Generally none

TREATMENT

No immunologic method available

IMMUNITY

A considerable degree of evanescent local immunity develops at the sites of active chancroid lesions and after weeks to months eventually leads to spontaneous healing There is no generalized chancre immunity such as that found in syphilis For this reason the chancroids are often *multiple* in contrast to the usually single syphilitic chancre Moreover autoinoculations with the products and secretions of the chancroidal ulcer will take and produce new chancroids whereas those from the syphilitic chancre will not The autoinoculation test is therefore a useful diagnostic measure for differentiating between chancroid and syphilitic chancre

Coccidioidomycosis (Coccidioidal Granuloma, "Valley Fever")

INCUBATION PERIOD

Generally not ascertainable—probably days to weeks

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

SKIN TEST —*Indication* —Skin tests with *coccidioidin* are generally of differential diagnostic value

Material —Coccidioidin prepared from cultures of Coccidioides immitis is not commercially available

Method —An intracutaneous injection of 0 1 cc coccidioidin is given in the flexor aspect of the forearm or arm The test is read at 24–48–72 hours

Description and Evaluation of Reaction —The reaction appears at 24–48 hours and usually persists two to four or more days The response is indicated by an erythematous papule or an infiltration about 1–2 cm in diameter The center of the papule is pustular at times A *positive* reaction indicates that the individual has been infected with C. immitis Specific skin sensitization results from either the skin infection or the systemic or pulmonary form (valley

fever California disease) A positive skin response does not nec essarily signify that the presenting signs of disease are caused by C immitis infection Once established the skin sensitivity lasts for years and perhaps for life

A *negative* reaction indicates that the patient has not been infected with C. immitis or is in a state of refractoriness or anergy or that the infection has taken place such a short time before that the skin has not yet become sensitive to coccidioidin In the third instance a later repetition of the test is of course indicated.

Contraindications and Dangers —Generally none

TREATMENT

Immunologic therapy is said to be of value in some cases How ever materials are not commercially available

IMMUNITY

Chancre immunity is probably present but there is apparently no regular increase in local or systemic resistance which would lead to spontaneous cure It is said that in some cases resistance can be in creased by hyposensitization with coccidioidin There are some cases presenting spontaneous involution of lesions followed by exacerba tions years later These remissions and recurrences may be due to immunologic changes produced by the fungus

Dermatitis Herpetiformis (Duhring s Disease)

PROPHYLAXIS

Avoidance of certain foods and drugs is of limited value It re duces the number of flare ups and recurrences in some cases of dermatitis herpetiformis Among the drugs are *iodides bromides* oc casionally others among the foods *chocolate fish shellfish nuts pork* etc Skin tests are usually of *no* value in discovery of the in gested agents which may act as trigger factors Observation of effects of avoidance (and of re exposure) is the only available method. It is not certain that the clinical reactions and exacerbations produced by trigger factors are attributable to an immunologic mechanism

skin and particularly against visceral toxic effects following and emanating from the skin infection

Drug Eruptions (Dermatitis Medicamentosa)

Drug* reactions form one of the most important chapters of modern medicine for both the causal drugs and the reactions they produce are today encountered in almost limitless number and variety The cutaneous changes produced by drugs range from the mildest itching or redness to the most disfiguring completely incapacitating long lasting and sometimes even fatal eruptions

There are a few drugs which—in therapeutic doses—produce allergic and other cutaneous changes in *practically all* those exposed (nirvanol disease atabrine discolorations) A few drugs have *never* been reported to cause such reactions (cascara sagrada saline cathartics castor oil) The largest category of drugs however includes those which cause reactions in only a certain percentage of persons exposed all others tolerating the usual doses without such reaction It must be recognized in such instances that the *reacting persons are significantly more sensitive* to the ill effects of the drug than are their fellows These drug reactions therefore are based on a *hypersensitivity* on the part of the patient

The mechanism of the causation of this hypersensitivity is often unknown Sometimes it is obvious that the drug has acted as a trigger factor activating a chain of circumstances which leads to the pathologic manifestation

A few examples in this category are the flare up of ordinary acne vulgaris after exposure to bromides or iodides activation or progression of tuberculosis after iodide therapy a Herxheimer reaction after arsenical or penicillin treatment eruptions of herpes simplex, herpes zoster and perhaps also lichen planus after treatment with arsenicals gold salts or other drugs and nodose and multiform erythemas after sulfonamide or salicylate therapy

*In this section the term drug is defined as any agent administered or otherwise employed to cure or to relieve this includes synthetic and other chemicals and biologic products

It is probable however that the largest group of drug eruptions includes those cases in which *the drug acts as an allergen* first specif ically sensitizing and then eliciting the allergic reaction in the sensi tized tissues Strictly speaking only this mechanism should be dis cussed under the heading of immunology There are however, so many drug reactions in which the exact basis of drug hypersensitivity is still obscure and so many in which immunologic and nonimmunologic mechanisms are combined that the present practical discussion must include the common forms of dermatologic drug reactions without excluding those based wholly or in part on nonimmunologic mechanisms

Drug eruptions often manifest the three classic periods known to be characteristic of immunologic sensitizations (p 255) Thus, in many cases there is the period of *refractoriness to sensitization,* during which drug exposures are tolerated for days months or years and then for no apparent reason seemingly identical exposures produce a specific sensitization The *incubation period of sensitization* can often be discerned in drug reactions the eruption or other sign of hypersensitivity becoming manifest from 5 to 21 days (usually 6–9 days) after the sensitizing drug exposure The *reaction time* or *latent period* is also a regular occurrence in drug eruptions the hypersensitive tissues evidencing an interval of seconds or minutes (urticarial reactions some fixed eruptions) to hours or days (eczematous eruptions nodose erythemas acneform morbilliform and scarlatiniform eruptions etc) between each exposure to the drug and the manifest clinical reaction

A consideration of the following facts may be helpful in the pre vention diagnosis and management of drug eruptions

1 In theory any and every drug may sensitize and produce drug reactions But like most allergens different drugs vary tremendously in their capacity to sensitize

2 In theory any drug may produce cutaneous reactions which are accompanied by reactions in other organs or by systemic manifesta tions *But different drugs show widely differing propensities for pro-*

ducing specific reactions in particular tissues organs or systems Thus, nirvanol and some sulfonamides are likely to produce skin eruptions accompanied by fever antisyphilitic arsenicals and gold are among the drugs which will most probably elicit purpuric skin reactions accompanied by hemorrhagic encephalopathy certain barbiturates (carbamides) are among the drugs most likely to cause the cutaneous purpuras of thrombocytopenia, etc.

All available evidence indicates that persons susceptible to *skin reactions* from *drugs are not necessarily those most susceptible to the ill effects of the same drug on other organs* This is of course of paramount practical importance

Thus the patient who develops an arsenical dermatitis is not necessarily the one most likely to suffer from hepatitis or blood dyscrasia from the same arsenical the patient who develops granulocytopenia or agranulocytosis from aminopyrine or gold or arsenicals is not necessarily the one most likely to present a fixed cutaneous eruption from the same medicament and the one who reacts to a sulfonamide with a skin eruption is not necessarily more likely to develop a purpura or granulocytopenia. These are only a few examples of the frequently observed localized and organ fixed nature of the hypersensitivity to drugs

3 A drug producing a reaction on one exposure will *not necessarily* produce reactions on each and every subsequent exposure In some instances the production of one or of several successive drug reactions appears to confer some degree of immunity or refractoriness to subsequent reaction to the same drug[3]

In some of these cases the "immunity appears to be long lasting or perhaps even permanent (nirvanol disease many sulfonamide reactions and some arsenical eruptions etc.) In other instances the refractoriness to reactions is only relative and temporary and is apparently of the same order as "hardening in eczematous contact type allergy

In still other cases the periods of susceptibility to drug reaction alter

[3]This fact of refractoriness or immunity to drug reactions sometimes following exposures to the offending drugs may at times serve as a prophylactic or desensitizing procedure Continued administration of small slowly increased doses of the drug allergen sometimes produces a degree of tolerance which permits the later use of therapeutic quantities of the drug.

nate without apparent reason or regularity with periods of refractori ness to reaction.

But in what is probably the largest group of drug reactions there is *no* apparent period of refractoriness and each and every adminis tration of the drug is followed by the particular drug reaction

4 Like all other allergic responses reactions to drugs depend largely on the degree of sensitivity of the shock tissues and the quantity of active available allergen reaching those tissues per unit of time

Sometimes incredibly small amounts of a drug suffice to produce severe and apparently maximal reactions. Sometimes the degree of re sponse appears to be graded to the quantity of exposure Sometimes larger exposures or the cumulative effects of repeated exposures are re quired to elicit the reaction.

In many cases of true allergy to drugs the exposure to quantities so small as to defy chemical analysis or other identification may produce maximal reactions This is one reason why all in vitro studies of a drug reaction may fail to reveal the eliciting drug. Moreover the chemical or other demonstration of the presence of a drug in the tissues or fluids of the patient is *not proof of the causal role* of that drug. Such demonstra tion proves only that the drug was encountered by the patient at some time previously and is still present—a fact which should be ascertainable in most cases by a careful taking of the history

5 Withdrawal of the offending drug is often followed by prompt improvement in the eruption it has elicited. In some cases however a considerable period—even many weeks—may elapse before im provement is noted And in some instances eruptions may *continue and even grow worse despite exclusion of further drug administration* (e g certain bromodermas iododermas and arsenical eruptions)

6 The route by which the drug reaches the sensitive tissues may or may not influence the result.

Thus a drug may produce a skin reaction on ingestion or on injection but fail to cause the reaction on external application, or vice versa. In other instances the same type of skin reaction takes place regardless of the route by which the drug reaches the skin. (One of our patients first

presented an eczematous contact type allergic dermatitis from *external application* of a quinine containing hair tonic a few months later the same type of dermatitis followed the *injection* of a quinine salt and still later an eczematous dermatitis appeared after the *ingestion* of a quinine containing cold cure)

7 As a rule a patient presents only one form of cutaneous re action to a drug However in some patients the same drug may produce several different forms of reaction

Thus a pustular or acneform reaction to iodides may be associated with an eczematoid reaction or with nodose erythema from the same drug or an eczematous eruption due to an arsenical may be associated with urti caria caused by the same drug These associated reactions may occur simultaneously or at different times

8 A patient hypersensitive to one drug may or may not be hyper sensitive to other drugs as well i e hypersensitivity to one drug does not necessarily indicate the existence of hypersensitivity to others However compared with normal persons persons who have a certain type of hypersensitivity to one drug appear somewhat more likely to develop *similar* forms of hypersensitivity to other drugs

When the same person is hypersensitive to two or more drugs either identical reactions are elicited by the different drugs or a dif ferent and characteristic form of reaction follows exposure to each drug Sometimes the reactions to the different drugs appear in the identical skin sites sometimes the different drugs elicit reactions in different sites

9 The drug hypersensitivity may be so *sharply specific* that there is complete tolerance even of compounds rather closely related to the allergenic drug More often there is distinct group hypersensi tivity and a patient hypersensitive to one drug will react to a greater or less degree to related compounds i.e to compounds con taining chemical groupings or characteristics identical with or simi lar to those of the original drug In other cases of hypersensitivity to a particular drug reactions will be elicited not only by a number

of other drugs but also by substances which appear to bear little or no relationship to the original compound (foods inhalants etc)

10 Almost every form of cutaneous change can on occasion be elicited or caused to exacerbate by a drug

Thus drug eruptions are capable of mimicking almost every dermatologic entity and they can range from mild evanescent itching to the most severe and sometimes fatal dermatoses Nevertheless drugs as a group tend to elicit certain types of skin reaction much more frequently than they do others and some drugs are much more inclined than are others to cause skin reactions Finally there are certain drugs which tend to produce only their own particular and characteristic forms of cutaneous response

The tendency of particular drugs to cause characteristic if not pathognomonic skin responses naturally forms an important basis for the etiologic diagnosis of skin eruptions Tables 17 and 18 are adapted from those originally compiled by R L. Mayer and present some of the common drug allergens and the reactions they most frequently produce Table 17 is intended to be of aid when the physician wishes to ascertain which drugs are most commonly responsible for a given form of cutaneous reaction Table 18 is intended for use when the physician has obtained evidence of exposure to a given drug or drugs and wishes to learn which cutaneous reactions are most likely to follow

PROPHYLAXIS

(See Prophylaxis and Treatment)

DIAGNOSIS

The following form the basis for diagnosis of drug eruptions

1 *A high index of suspicion* (Stokes) *(a)* Always suspect the possibility of a drug reaction in any eruption of unknown cause and be doubly suspicious of drugs in all otherwise inexplicable chronic or recurrent dermatoses *(b)* Be particularly suspicious of drugs in the eruptions listed in Table 17

TABLE 17 —SOME COMMON DERMATOSES AND THEIR MOST FREQUENTLY CAUSAL DRUGS

1 Acneform furunculoid and erysipelas like eruptions (bromides iodides oils tars etc.)
2 Eczematous eruptions with erythema papulation vesiculation weeping and scaling (quinine procaine other local anesthetics ephedrine mercurials formalin sulfonamides penicillin arsphenamines atabrine etc)
3 Erythema multiforme like eruptions (phenolphthalein antipyrine salicylates barbiturates other soporifics sulfonamides penicillin etc)
4 Erythema nodosum like eruptions (iodides bromides salicylates sulfonamides)
5 Fixed eruptions i e fixed circumscribed erythematous edematous or bullous and polychromatic pigmented eruptions (phenolphthalein antipyrine phenacetin barbiturates salicylates the arsphenamines atabrine gold sulfonamides) All so-called fixed eruptions have in common the *fixed* circumscribed nature of the *site* of sensitivity and reaction and thus all tend to recur in situ
6 Lichenoid and lichen planus like eruptions (arsenic arsphenamines atabrine gold amphetamine sulfate etc) (atopic dermatitis-like eruptions?)
7 *Pemphigoid and ulcerating and vegetating eruptions (bromides* iodides sulfonamides)
8 Purpuric eruptions (iodides arsphenamines particularly sulfarsphenamine carbamides [sedormid] barbiturates balsams sulfonamides etc.)
9 Scaly eruptions purely erythematous or scarlatiniform and morbilliform dermatitis exfoliativa (arsenicals belladonna balsams heavy metals nirvanol penicillin salicylates sulfonamides etc.)
10 Urticaria and angioneurotic edema (salicylates barbiturates sulfonamides penicillin belladonna atropine iodides bromides the opium group arsenicals phenolphthalein amphetamine sulfate etc)

Th d the follow g table are b sed o S l berger M B *Dermatol g Allergy* (Sp gfi ld Ill, Charles C Thoma P bl sh 1940)

2 *A careful and indefatigable taking of a sharply focused history* This must include questions concerning possible exposures to the innumerable and varied forms and disguises in which suspected drugs may be encountered All remedies applied ingested injected inhaled or inserted must be considered in the search All possible occult exposures should be investigated The patient must be questioned systematically skilfully and *not once but over and over again* History

taking is not completed until either the suspected drug or some other cause of the eruption has been discovered and proved guilty The direction of questioning is of course indicated to a considerable extent by previous information and by the clinical picture (Table 17)

3 *Avoidance of exposures to drugs which are suspects and observation of the effects of avoidance* In every persistent dermatosis of unknown origin the avoidance of all drugs not absolutely necessary to life or health is an essential diagnostic measure and often also the most effective therapeutic procedure

IDENTIFICATION OF ELICITING DRUGS—The eliciting drug is discovered by the following steps

1 *Recognition of the eruption as one which is attributable to a particular drug or drugs* (Tables 17 and 18)

2 *Evidence that actual exposure to the suspected drug or drugs occurred at a time adequate for eliciting the eruption*

Usually a few minutes to hours (up to 24 or more hours) elapse between drug exposure and the manifestation of reaction. This statement does not apply to cases evidencing refractoriness to sensitization in which ill effects may appear only after days, weeks or years of exposure Nor does it apply to cases first acquiring the sensitization, in which the 5–28 day incubation period follows the first sensitizing exposure

3 *Observation of improvement or cure following avoidance of the suspected drug or drugs*

Sometimes drug eruptions persist or even progress for weeks months or years despite apparent avoidance of the causal drugs (e g. arsenic bromides iodides) Nevertheless the majority of patients with drug eruptions improve within a reasonable time after avoidance of exposure (a few days or a week or so)

4 *Observation of recurrences or exacerbations of the eruption following re exposure to the suspected drug or drugs*

Observation of effects of chance clinical re exposures is often helpful in this respect. *Deliberate exposures are generally unnecessary* for in most cases the aforementioned three steps will suffice to prove or dis

TABLE 18 —COMMON DRUGS CAUSING ERUPTIONS AND THE CHARACTERISTIC FORMS THEY PRODUCE

Antipyrine

- Erythema multiforme like eruptions
- Fixed eruptions (similar to those due to phenolphthalein)
- Hemorrhagic eruptions
- Morbilliform eruptions
- Pemphigoid (bullous and vesicular) eruptions
- Scarlatiniform eruptions
- Urticarial eruptions

Arsenic

- Adiposities
- Bowen like precanceroses
- Corns
- Ecchymoses
- Eczematous and eczematoid eruptions (localized and generalized)
- Epitheliomas (multiple superficial)
- Erythemas (palmar and plantar)
- Erythema multiforme like eruptions
- Erythema nodosum
- Erythrodermas
- Exfoliative dermatitis (localized and generalized)
- Follicular hyperkeratoses
- Herpes zoster (ordinary and gangrenous)
- Hyperhidrosis
- Keratoses (palmar plantar and other)
- Leukodermas (localized and generalized)
- Lichen planus like eruptions
- Loss of hair loss of nails
- Melanodermas (localized and generalized)
- Mucous membrane changes (conjunctivitis pharyngitis rhinitis stomatitis)
- Necrosis and gangrene
- Neurologic changes—neuritis neuralgia formication other paresthesias hyperesthesia pain
- Parapsoriasis like eruptions
- Pemphigoid (bullous) eruptions
- Perforated septums (usually exogenous from inhalation of arsenic containing dust)
- Pityriasis rosea like eruptions
- Psoriasiform eruptions
- Purpuric eruptions (particularly bullous and hemorrhagic dermatoses)
- Scleroderma like eruptions
- Ungual changes
- Urticaria
- Vasomotor disturbances (pallor blushing Raynaud's disease" acrodynias)
- Warts

Th asterisk preceding the descripti e m denotes th t the ma festa n s among the more common of the react ons produced by the part cul r drug.

TABLE 18 CONTINUED—COMMON DRUGS CAUSING ERUPTIONS AND THE CHARACTERISTIC FORMS THEY PRODUCE

Atabrine (Quinacrine hydrochloride)
- Alopecias (patchy)
- Eczematous and eczematoid eruptions
- Exfoliating erythrodermas
- Fixed eruptions
- Lichen planus like eruptions
- Lupus erythematosus like eruptions
- Pigmented and depigmented eruptions
- Poikiloderma like eruptions
- Psychotic states
- Ungual dystrophies

Bromine and Bromides
- Acneform eruptions
- Ecthyma like eruptions
- Eczematous and eczematoid eruptions
- Erythema multiforme like eruptions
- Erythema nodosum like eruptions
- Furunculosis like eruptions
- Generalized exanthems (roseola like rubeola like and scarlatiniform eruptions)
- Pemphigoid (bullous and vesicular) eruptions (sometimes fatal)
- Tuberous and fungating, neoplastic tumor like eruptions (sometimes fatal)
- Ulcerative eruptions (sometimes fatal)
- Urticarial eruptions

The circumscribed bromodermas have been reported to simulate
- Deep and ulcerative fungous infections (kerion celsi) (coccidioidosis blastomycosis chromoblastomycosis sporotrichosis)
- Erythema nodosum
- Neoplasms
- Pemphigus vegetans (sometimes fatal)
- Rhinophyma, rosacea
- Syphiloderms (ulcerative tertiary syphilids of skin or mucous membranes)
- Tuberculosis (erythema induratum)

Iodine and Iodides
- Acneform eruptions
- Angioneurotic edemas (sometimes fatal)
- Eczematous and eczematoid eruptions
- Edemas (circumscribed and diffuse)
- Erythemas (circumscribed and diffuse)
- Erythema multiforme like eruptions
- Erythema nodosum like eruptions
- Furunculosis like eruptions
- Gangrenous eruptions
- Generalized exanthems (roseola like rubeola like and scarlatiniform eruptions)

TABLE 18 CONTINUED—COMMON DRUGS CAUSING ERUPTIONS AND THE CHARACTERISTIC FORMS THEY PRODUCE

Iodine and Iodides (Cont)
- Mycosis fungoides like eruptions
- Pemphigoid (bullous and vesicular) eruptions (sometimes fatal)
- Purpuric and hemorrhagic eruptions
- Pustular (vaccinia and variola like) eruptions (sometimes fatal)
- Tuberous and fungating neoplastic tumor like eruptions (sometimes fatal)
- The circumscribed iododermas have been reported to simulate
  - Blastomycosis (sometimes fatal)
  - Syphilis (sometimes fatal)
  - Tuberculosis (sometimes fatal)

Penicillin
- Angioneurotic edema
- Eczematous and eczematoid eruptions (contact type)
- Exanthems with joint swellings and other manifestations resembling serum sickness
- Morbilliform eruptions
- Pompholyx and dyshidrosis like eruptions of the hands and feet
- Urticarial eruptions

Phenolphthalein
- Eczematous and eczematoid eruptions (contact type)
- Erythema multiforme like eruptions
- Fixed eruptions of characteristic course and appearance
- Pemphigoid (bullous and vesicular) eruptions
- Urticarial eruptions

Pyramidon
- In general like antipyrine
- Blood dyscrasias (sometimes fatal)

Quinine
- Bullous and pemphigoid lesions of the mucous membranes (sometimes fatal)
- Eczematous and eczematoid eruptions
- Edemas and erythemas
- Exfoliating erythrodermas
- Fixed eruptions
- Melanodermas
- Purpuric eruptions (sometimes fatal)
- (Respiratory symptoms [asthma and rhinitis])
- Scarlatiniform and morbilliform eruptions
- Urticarial eruptions

Salicylates
- Angioneurotic edema
- Asthma
- Conjunctivitis

TABLE 18 CONTINUED—COMMON DRUGS CAUSING ERUPTIONS AND THE CHARACTERISTIC FORMS THEY PRODUCE

Salicylates (Cont)
Constitutional reactions (sometimes fatal)
Eczematous and eczematoid eruptions (contact type)
Edemas
Erythemas
Erythema multiforme like eruptions
Erythema nodosum like eruptions
Fixed eruptions
Morbilliform eruptions
Pemphigoid (bullous and vesicular) eruptions (sometimes fatal)
Pompholyx and dyshidrosis like eruptions
(Rhinitis)
Scarlatiniform eruptions
Urticarial eruptions
Beware of salicylates in atopic patients and especially in asthmatics!

Soporifics—Barbiturates and other urea derivatives sulfonal etc
Eczematous and eczematoid eruptions (contact type)
Erythema multiforme like eruptions
Erythrodermas
Exfoliative dermatitis
Fixed eruptions
General manifestations blood dyscrasias (sometimes fatal)
Morbilliform eruptions
Mucous membrane eruptions (multiform and bullous)
Nirvanol disease
Pemphigoid (bullous and vesicular) eruptions
Purpuric and hemorrhagic eruptions
Scarlatiniform eruptions
Urticarial eruptions

Sulfonamides
Angioneurotic edema
Eczematous and eczematoid eruptions (contact type)
Erythema multiforme-like eruptions
Erythema nodosum like eruptions
Exfoliative dermatitis
Fixed eruptions
Infectious eczematoid dermatitis like eruptions
Morbilliform eruptions
Pemphigoid (bullous and vesicular) eruptions
Pemphigus foliaceous like eruptions
Purpuric eruptions
Pustular and varioliform eruptions
Scarlatiniform eruptions
Serum sickness like reactions
Urticarial eruptions

prove the role of the drug Deliberate exposures are *not without risk* and they *are not infallible* tests because the patient may well be in a phase of refractoriness and fail to react to exposure to the drug which actually caused the original eruption

1 In most drug reactions skin tests are useless in attempts to discover the eliciting drugs

2 Only in exceptional instances—such as in true eczematous and occasionally in true urticarial drug eruptions—will the appropriate skin test prove valuable

3 In most drug reactions no specific serologic changes or circulating antibodies can be discovered by available methods

4 In most drug reactions demonstration of the presence of a drug in the fluids or tissues of the patient does not constitute proof of the causal role of that drug It proves only that the drug was encountered by the patient

5 In most drug reactions failure to demonstrate a drug in the fluids or tissues of the patient does not exonerate the drug as a possible causal agent It proves only that the drug is not present in demonstrable quantity or form at the time of examination

Skin Tests—Skin tests are generally of *no practical value* in the search for eliciting agents of drug reactions In the following few exceptions skin tests may occasionally be of some assistance

1 *In true eczematous allergic contact type eruptions from drugs* Regardless of the route of drug administration patch tests may be used here just as in cases of eczematous dermatitis from external agents

2 *In truly urticarial allergic eruptions from drugs* Here scratch or intracutaneous tests for immediate wheal reactions may be used just as in cases of allergic urticaria However the results are subject to the same serious limitations Moreover many drugs (e g morphine codeine atropine pilocarpine physostigmine histamine) are *primarily irritant or urticariogenic agents* and drugs and vehicles which are primarily urticariogenic cannot be used for skin testing without first being diluted to concentrations which produce no whealing in a control series of normal skins

PROPHYLAXIS AND TREATMENT

The general management of drug eruptions can be divided into the following four methods of approach

1 *Treatment of the manifestation* The treatment is that which is usually effective against the particular clinical skin lesion. Acne form eruptions are treated like acnes using topical remedies and x ray furunculoid eruptions are treated like furunculosis Patients with urticarial eruptions are given adrenalin or antihistaminic agents (Pyribenzamine or Benadryl) and the eruption is treated like urticaria from other causes Drug pruritus is treated symptomatically like itching from other causes etc

Of course these methods are all symptomatic Although often of great benefit they cannot be expected to give pe manent relief unless the causal agents have been discovered and removed

2 *Treatment directed toward elimination neutralization or in activation of the drug* Here the accepted measures for speeding up elimination of the drug from the body are instituted Fluids are forced emetics and purges given etc Or the accepted drug antidotes precipitants chemical neutralizers etc are administered (e g BAL for arsenic and mercury) These measures though sometimes strikingly effective are often of negligible value *(a)* because the quantities of drug necessary to produce the allergic reaction are often minute *(b)* because the drug eliciting the reaction is usually fixed to the tissues and often conjugated with other molecules before the therapy can be instituted and *(c)* because the drug has often set in

motion mechanisms of damage which will proceed without further influence or presence of the drug

3 *Measures which may tend to increase resistance through improvement of general health and the improved function of all organs* These consist of common medical procedures including any otherwise indicated endocrinologic measures nutritional improvements (vitamins) elimination of infections combating and preventing fatigue and psychic and emotional disturbances etc. Although such measures should not be neglected they are usually of limited value or are difficult to evaluate in regard to their effects on drug eruptions

4 *Immunologic or causal management* This approach is usually of the greatest value As none of the available procedures of specific hyposensitization are generally effective practical immunologic *prophylaxis and treatment both depend on the fullest possible avoidance or reduction of exposures to the eliciting drug allergens*

AVOIDANCE OR REDUCTION OF EXPOSURES TO DRUGS —Under the usual conditions of modern life virtually every individual is almost constantly exposed to countless different allergenic drugs (in the widest sense of the term) These exposures may be overt in the form of prescribed and/or proprietary medicaments or they may be occult, in the form of drugs or substances *usually* used to prevent, heal or relieve which are contained in foods preservatives insecticides antimold and antimildew preparations rust proofing water proofing and fire proofing preparations toilet and cosmetic articles dyes plastics articles of ornamentation of clothing of furnishings of games sports etc. Unfortunately so many everyday articles contain traces of chemicals which are actually used as drugs or which are related to drugs that the detection of such sources of exposures becomes a most difficult and highly specialized and technical problem

Because of the many occult exposures as well as the numerous exposures to actual medicaments the *physician should suspect drugs*

as possible eliciting agents in every case of obscure etiology and in every inexplicable chronic or recurrent condition

And in every such case the patient should be forbidden the use of all drugs not essential to his life or health or to public health

When a patient with a suspected drug reaction presents *imperative* indications for use of a certain *type* of drug the physician should attempt to replace the particular drug suspected of causing the reaction by some other compound or combination of compounds having a different structure but similar effects The following list[4] may be of some value in these attempts at substitution

For *barbiturates* attempt to substitute

Alcohol	Demerol
Bromides	Dover s powder
Bromovalerianate	Morphine
Bromural	Pantopon
Chloral hydrate	Paraldehyde
Chloretone	Salicylates
Chlorobutanol	Sulfonal
Codeine	Urethane

For *antisyphilitic arsenicals* attempt to substitute

Bismuth
Iodides
Mercury
Penicillin

For *salicylates* attempt to substitute

Acetanilid	Antipyrine
Acetophenetidin	Bromides
Aminopyrine	Quinine

For *aminopyrine* attempt to substitute

Acetanilid	Demerol
Acetophenetidin	Morphine
Bromides	Pantopon
Codeine	Salicylates

For *phenolphthalein* attempt to substitute

Agar	Jalap
Aloe	Milk of magnesia
Bile salts	Mineral oil
Calomel	Podophyllin
Cascara	Rhubarb
Castor oil	Saline cathartics
C trate of magnesia	Senna
Enemas	Suppositories

For *quinine* attempt to subst tute atabrine or the newer antimalarials (chloroquine etc)

[4]The subst tutes are listed in alphabetical order and *not* in order of preference

For *atabrine* attempt to substitute quinine or the newer antimalarials (chloroquine etc)

For *bromides* attempt to substitute

- Alcohol
- Barbituric acid derivatives e g
  - Allonal
  - Alurate
  - Amytal
  - Amytal sodium
  - Barbital
  - Barbital sodium
  - Dial
  - Ipral
  - Pentobarbital sodium
  - Pentothal sodium
  - Phanodorn
  - Phenobarbital
  - Phenobarbital sodium
  - Seconal
  - Veronal
- Chloral hydrate
- Chloretone
- Chlorobutanol
- Demerol
- Dover s powder
- Morphine
- Pantopon
- Paraldehyde
- Sulfonal
- Urethane

For *sulfonamides* attempt to substitute other antibacterial agents penicillin streptomycin other antibiotics

For *penicillin* attempt to substitute other antibacterial agents streptomycin other antibiotics sulfonamides

Attempts at substitution are not always satisfactory or successful Most failures occur either because the substituted drug is not as acceptable or as effective as the one used originally or because the substituted drug also produces untoward reactions In some cases the former difficulty may be overcome and a satisfactory surrogate found by substituting a drug more or less closely related to the original medicament This will be successful in those patients in whom the hypersensitivity is so sharply specific that it distinguishes between close chemical relatives Thus in some patients certain barbiturates will cause reactions whereas other barbiturates or carbamides will be tolerated certain organic arsenicals will cause reactions whereas other organic arsenicals will be tolerated or certain sulfonamides will cause reactions and others not

Whenever possible the drugs chosen as substitutes should be those known to possess *less of a tendency to cause reactions than the original drug* Particular caution is of course required when the drug reaction was a serious one such as a constitutional reaction

blood dyscrasia hepatic damage hemorrhagic pemphigoid or ex foliative dermatosis etc

In all attempts at drug substitution great caution is to be exercised This is doubly true when the substitute is chemically related to the previous offender It is always wise *to start with very small* doses of the substitute First give only fractions of the therapeutic dose and observe the effect. If no untoward reactions occur the dose may then be increased gradually and slowly In case of a possible explosive reaction to ingested drugs (e g salicylates in atopic individuals) it may be wise to let the patient hold the medicament in his mouth (not swallow it) so that he may spit the remainder out at the first indication of reaction If a possible explosive reaction is feared from drugs generally administered by subcutaneous injection it is wise to observe the precautions described in the sections on skin testing and injection of allergens *Only a small amount is injected into the distal portion of an extremity with a tourniquet in place proximal to the injection site and ready to be tightened to slow down absorption* The absorption may then be regulated somewhat by alternate tightening and loosening of the tourniquet. Of course the recognized antidotes and therapeutic agents (epinephrine etc) should also be available and should be administered when required

READMINISTRATION OF DRUGS WHICH HAVE ELICITED REACTIONS —Administration of a particular drug is sometimes essential even though it is known or presumed to have elicited an untoward reaction. At least if there is no adequate substitute for the drug if there is a se ious indication for its administration and if the reaction in question was not too dangerous a one the physician may judge the attempt at readministration to be justified.

REFRACTORINESS TO DRUG REACTION SPECIFIC HYPOSENSITIZATION —In this connection it is to be noted that although many patients react to each administration others do not react on readministration of the very drug which first caused reaction Such supervening *refractoriness* to reaction is the rule in nirvanol rashes

many sulfonamide rashes some arsenical eruptions and in many cases of morbilliform and scarlatiniform lichenoid and herpetiform reactions from various drugs Indeed, in numerous instances the drug reaction recedes and the patient recovers during and despite the *continued drug administration* It appears likely that in some of these patients the continued administration of the drug allergen has succeeded in producing a specific hyposensitization with a resulting period of immunity or refractoriness to drug reaction

Even though there are many instances in which the readministration or continued administration of a suspected drug is not followed by ill effects the giving of a drug which has once caused an untoward reaction is always a delicate potentially dangerous undertaking It must always be approached with circumspection and a full realization of the hazards All precautions must be fully observed including the initial very small quantities the gradual increase of dose the close noting of effects and the availability of all known preventive therapeutic and antidotal measures And above all the physician must have the conviction that the particular drug is *necessary*, that it is for all practical purposes *irreplaceable* and that its administration is fully *justified despite the risks*

PROPHYLACTIC SKIN TESTS —*With the exception of the procedures described under eczematous eruptions and urticarial eruptions it is in general impossible to predict by skin test or by other type of preceding immunologic procedure whether an individual will or will not evidence hypersensitivity to a given drug Nor do responses to skin tests or to other tests indicate the type of clinical reaction which may occur*

PROPHYLAXIS BASED ON HISTORY —Only the most complete and detailed history based on questions directed to discover previous drug reactions (p 284) will enable the physician to discover evidences of possible sensitivity to certain drugs and thus to eschew their use

PROPHYLAXIS BASED ON CLINICAL APPEARANCE OF SKIN — There is some evidence indicating that patients presenting the dermatologic conditions listed in Table 19 are on the whole inclined to have an increased susceptibility to particular forms of reaction from drugs

TABLE 19—DERMATOLOGIC CONDITIONS IN WHICH PATIENTS TEND TO REACT TO PARTICULAR DRUGS

1 Acne and acneform eruptions and furuncles more susceptible to iodides bromides androgens other steroid hormones (and certain foods—chocolate shellfish etc.)
2 Atopic conditions more susceptible to salicylates
3 Dermatitis herpetiformis more susceptible to iodides bromides (and certain foods)
4 Hypertrichosis more susceptible to androgen c substances
5 Moniliasis and moniliids more susceptible to iodides and bromides
6 Purpuric and hemorrhagic conditions more susceptible to barbiturates arsenicals gold salts sulfonamides
7 Recurrent herpes simplex more susceptible to iodides bromides (and certain foods—chocolate shellfish caviar nuts)
8 Seborrheic conditions intertrigos infected and impetiginized eczematoid eruptions more susceptible to antisyphilitic arsenicals gold salts penicillin sulfonamides
9 Urticarial eruptions more susceptible to salicylates iodides bromides and a great variety of other drugs and to foods

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M e suscept ble th a g oup of perso s witho t these derm tologic cha ges r h story f these ch ges

MEASURES INTENDED TO REDUCE DEGREE OF DRUG INTOLERANCE —Because of the frequent occurrence of spontaneous unpredictable and erratic fluctuations in the levels of drug susceptibility all measures reputed to decrease the degree of drug intolerance are difficult to evaluate It has been held that administration of a fractional dose of a drug shortly before giving the full dose tends to reduce the untoward reactions This method, known as *skeptophylaxis* has been particularly in vogue for the administration of foreign serum It is not yet known whether the effect is an actual hyposensitization

As previously mentioned it appears likely that in certain instances repeated or continued exposures to small or ascending doses of the allergenic drug can produce specific hyposensitization and thus increase the patient s tolerance It also seems possible that continued administration of small amounts may in some cases *prevent* the development of a drug sensitivity

The following *nonspecific* measures generally do no harm and may perhaps in some instances increase the patient s tolerance to certain drugs

1 The slow administration of drugs which are injected intravenously

2 The administration of drugs in high dilution by drip method

3 Injections of large amounts of *crude* solution of liver Crude liver extract (Parke Davis Lilly) is given intramuscularly in 5 cc. doses three times weekly (or when suitable extracts are available intravenously) This may be tried to increase tolerance particularly to arsenicals gold salts bismuth naphuride (germanin) and other hepatotoxic drugs

4 Ascorbic acid 500–1 000 mg daily by mouth may be tried particularly in drug intolerance associated with purpuric or hemorrhagic tendency

5 Menadione (vitamin K) 2 mg in oil is given by deep intramuscular injection or 2 mg is given orally This daily dosage should not be continued for more than four weeks This treatment may be tried in drug intolerance associated with purpuric or hemorrhagic tendency

6 Nicotinamide 200 mg daily by mouth may be tried particularly in drug intolerance associated with increased sensitivity to light

7 Thyroid extract may be given but should not be prescribed unless the basal metabolic rate is below normal or at a low normal level and the patient can be observed regularly while under treatment

8 Adrenal cortical extract 100–500 units or desoxycorticosterone 3–5 mg is administered subcutaneously daily and is supplemented with large amounts of sodium chloride

9 Autohemotherapy in which 10–20 cc of the patient s blood is drawn from the cubital vein and at once injected deep intramuscularly into the buttock, may be tried in urticarial drug eruptions This treatment should be repeated twice weekly or every other day for a total of 6–8–10 injections

10 Measures to eliminate general medical conditions sometimes considered as contributory to drug intolerance are (1) elimination of foci of infection (in teeth, tonsils sinuses prostate in fungous or other infections of skin, etc.) (2) control of liver and gallbladder disease kidney disease gastrointestinal disease intestinal parasites anemias blood dyscrasias etc., diabetes mellitus endocrine disturbances psycho genic and emotional factors etc

11 Measures to eliminate skin conditions which are in some cases contributory to drug intolerance include (1) orthodox treatment of excessively dry or oily skin, of wet soft skin of hyperhidrosis etc. (2) orthodox treatment of acne seborrhea, fungous infections atopic derma toses purpuras pyodermas psoriasis lichen planus dermatitis herpeti formis herpes simplex

12 Antihistaminic substances 25–50 mg three to four or eight times daily by mouth of Pyribenzamine (Ciba) or Benadryl (Parke Davis) can be tried particularly in urticarial and angioneurotic edema like drug eruptions in other drug eruptions with urticarial features and in pruritus from drugs Until more experience has been gained blood counts and urine examinations appear to be indicated at regular intervals (weekly) in patients who are being treated with these drugs

These measures are mentioned here not only because of their potential value but because their mechanism of action may well include a number of immunologic effects

Eczematous Contact-Type Allergic Dermatitis

This section deals with allergic forms of contact dermatitis con tact type eczematous dermatitis contact eczema and dermatitis vene nata including allergic plant dermatitis and allergic industrial or occupational dermatitis

Eczema is a term denoting a disease entity based on a morpho logic concept Thus eczematous changes of the skin can be caused by a great variety of agents and mechanisms Many eczemas are due to unknown causes some to fungi viruses and other infecting agents and some to physical influences (friction heat light etc)

Perhaps the largest group of acute and subacute eczemas is attrib

utable to allergic sensitization and exposure of the skin (epithe lium?) to more or less simple chemical allergens Some of the ecze matogenic allergens can produce this form of eczematous eruption whether they reach the skin from within or from without but in the vast majority of cases the allergen produces the eczematous reaction by direct (external) contact with the skin Because these eruptions are generally but not always elicited by external contact we have chosen here to call them by the cumbersome yet clearly descriptive term eczematous contact type allergic dermatitis ' or contact type dermatitis for short

Sensitization can begin to develop on first exposure to an allergen Or the individual may remain immune to sensitization for periods which vary greatly in length (period of refractoriness to sensitization) The *incubation period of sensitization* is often not ascertainable in individual cases but it is usually 6–28 or more days The *reaction time of sensitivity* (the time required for a previously sensitized indi vidual to manifest a reaction on exposure to an adequate amount of the eliciting allergen) may vary from a few minutes to several days The usual reaction time is 24–72 hours When the allergen is ap plied as a patch test the reaction is usually read at 48 hours or later

PROPHYLAXIS

The accepted measures of avoidance and reduction of allergenic exposures are in general more effective than any form of immuno logic prophylaxis Whereas specific hyposensitizing measures may some day prove useful the specific prophylactic methods available at present are of *little or no value* in most cases of eczematous dermatitis However certain cases and types of eczematous eruptions appear to be in some measure preventable by specific immunologic measures Notable among these are eczematous eruptions due to hy persensitivity to certain *plants, plant oils, certain vegetable oils, flowers and their derivatives*

As a guide to the measures employed in this group the specific hyposensitizing procedures in allergic contact type dermatitis from plants and in particular from poison ivy will be given in detail

HYPOSENSITIZING PROCEDURES FOR PROPHYLAXIS OF PLANT DERMATITIS —The immunologic prophylaxis of poison ivy and other plant dermatitides by administration of extracts containing the specific allergens should be attempted only when clearly indicated The administration of the specific extracts must be begun some time preferably several months before the expected exposure

Indications —Specific measures of hyposensitization may be of value in the following instances

a) In an individual who is strongly hypersensitive and who has repeatedly suffered severe eczematous dermatitis following exposures to a certain plant when future exposures cannot be avoided.

b) In instances in which a large population (military groups labor groups camps etc) will inevitably be exposed to a plant which notoriously produces a high incidence of severe allergic eczematous dermatitis

(In the case of *(a)* the specific excitant is administered to the hypersensitive individual before his exposures whereas in *(b)*, the specific excitant is administered to the entire group regardless of individual hypersensitivity)

Materials —The poison ivy plant is the most common cause of plant dermatitis in the United States There is good evidence that the plants popularly known as poison ivy poison oak and poison sumac contain common allergenic principles However a number of firms prepare separate extracts of these plants. The following materials are among those commercially available for specific prophylactic hyposensitization. (We do not favor the use of extracts containing local anesthetics The anesthetic probably does no good and merely presents an additional substance capable of sensitizing)

For oral administration

Cutter Laboratories Poisonivi (concentrated) or Poisonok (concentrated) in 13 cc. dropper stoppered bottle *Dosage* (prophylactic) first day 1 drop in half a glass of water increase by 1 drop each day until the 10 drop level is reached and finish contents of bottle with the 10 drop daily dose

Contents of a single bottle taken at the beginning of each season is said to provide sufficient protection for most individuals.

Dermatologic Prescription Laboratories (San Francisco) Rhustabs (dividable tablets) in packages of 50 each tablet containing 2 500 dermatitant units of an oleoresin obtained from poison oak Rhuscaps (capsules) in packages of 50 each capsule containing 5 000 dermatitant units of an oleoresin obtained from poison oak *Dosage* 1 Rhustab daily for 10 days followed by 1 twice daily and then 1 three times daily for 10 days then 1 Rhuscap three times daily for 100 doses

Graham Laboratories (Dallas) Rhusresin (Oral Poison Ivy Resin) in sets of three 1 oz. dropper bottles containing 1 100 1 50 and 1 25 concentrations of ether extracted ivy oleoresin diluted in corn oil and sufficient capsules for complete treatment *Dosage* initial dose is 1 drop of the 1 100 dilution in a gelatin capsule daily for one week then 2 drops daily for one week then increase the number of daily drops as rapidly as tolerance permits After the contents of the 1 oz bottle of the 1 100 dilution have been taken, start the 1 50 dilution The first dose is one half the final dose of the 1 100 dilution then increase the number of daily drops as rapidly as tolerance permits After the contents of the 1 oz bottle of the 1 50 dilution have been taken start the 1 25 dilution The dosage is one half the maximal daily dose of the previous dilution increase the dose as tolerance permits The contents of all three bottles in the package must be taken to achieve maximal protection

National Drug Co Tincture of Rhus Tox or Tincture of Rhus Venenata in 1 oz. dropper bottles *Dosage* 5 drops in half a glass of water after each meal each subsequent dose is increased 1 drop until 15 drops are taken after each meal suggested length of treatment is one month or longer

For administration by injection

Abbott Laboratories Poison Ivy Extract (solution in sweet almond and peanut oils) in packages of two 1 cc. ampules

Cutter Laboratories Toxivi or Toxok (solution in alcohol) Toxivi packages contain three 1 cc. doses in syringe with three sterile needles Toxok, two 1 cc. vials and one 20 cc. vial with syringe and three sterile needles Toxok Concentrate two 0 1 cc. vials of material and two vials of diluent.

Hollister Stier Laboratories Poison Ivy Extract or Poison Oak Extract in packages of 5 ampules each containing 0 2 cc. of alcohol extract with 5 ampules of sterile salt solution for dilution immediately before administration

Lederle Laboratories Inc. Poison Ivy Extract or Poison Oak Extract (solution in almond oil) in packages of one and two 1 cc. vials

Mulford Colloid Laboratories Rhus Tox Antigen in pack ages of four 1 cc. ampule vials contains 0 4 per cent procaine hydrochloride

Parke Davis & Co Poison Ivy Extract (solution in al mond oil) in packages of six 1 cc. ampules

Pitman Moore Co Poison Ivy Extract (solution in alco-hol) in packages of one 1 cc. vial plus three 0 9 cc. vials of diluent consisting of isotonic salt solution containing procaine hydrochloride 0 5 per cent and chlorobutanol 0 4 per cent.

Sharp & Dohme Inc. 'Ivyol Poison Ivy Extract (solution in olive oil with 2 per cent camphor) in packages of one and four 0 5 cc vials

E R. Squibb & Sons Poison Ivy Extract or Poison Oak Extract in packages of 3 cc. vials (for preseasonal treatment of at least 10 injections) extract to be diluted with sterile distilled water according to directions

Other Contact Type Eczematogenic Allergens—Allergenic oils of some other plants and of foods can be obtained on special request from some of the aforementioned firms

Methods—Oral Administration. Prophylaxis by means of oral administration of poison ivy extracts or of the extracts of other plants or allergenic oils should be started about three to four months before the expected period of exposure and should be continued

throughout this period If during the hyposensitizing procedure clinical exposures to the allergenic material produce reactions which clearly demonstrate the measure s ineffectiveness the attempt at hyposensitization should be stopped (For instructions regarding details of dosage etc see under the individual commercial products)

Administration by Injection Prophylaxis by means of injection of poison ivy poison oak and poison sumac extracts should be started about four weeks before the expected exposure It is usual to give two intramuscular injections of 1 cc each with a two week interval between injections In patients with an extreme sensitivity to poison ivy prophylaxis should be started about eight weeks before the expected exposure four intramuscular injections usually consisting of 0 25 cc 0 5 cc 1 cc and 1 cc are given at two week intervals (The pamphlet enclosed in the package of the particular extract should be consulted for dosage Each firm has its own method of preparing poison ivy extracts and the quantities of allergenic principle and probably also the type of allergenic principles present differ greatly in the different extracts)

Prophylaxis by intramuscular injections of extracts of other plant and allergenic oils which at present are not usually commercially available in the United States should be started about four months before the expected exposure It is usual to give intramuscular injections in ascending doses of 0 1 0 2 0 3 and 0 5 cc at first one week apart and then at two to four week intervals throughout the period of clinical exposure

Experts still disagree radically about the general value of prophylactic injections and there are no set rules regarding the number of injections to be given or the period of time for which the injections should be continued Each case must be judged and managed individually The dosage schedule and period of treatment should be adjusted according to the beneficial effects or the untoward reactions produced by the treatment As soon as the patient appears to be clinically protected the intervals between injections should be gradually lengthened. Finally a trial withdrawal of treatment should be

made and resumption instituted only when there is evidence of re newed clinical sensitivity

The usual precautions in giving intramuscular injections and in particular those used to prevent contact of the injected excitant with the skin (p 83) must be observed. It is our opinion that the injections should not be continued if despite the usual series of in jections the patient gives no evidence of protection at the time of his first ensuing clinical exposure

Contraindications and Dangers—In general prophylactic hyposensitization should not be attempted in the presence of active dermatitis Flare ups exacerbations spread and prolongation of the dermatitis may result. Both the oral and the injection measures should be *stopped* if serious or disagreeable reactions are evident or appear imminent.

Certain by-effects appear quite frequently The most common of these are (1) flare ups at sites of old dermatitis (2) new areas of dermatitis and vesication particularly on the hands (3) dermatitis or other inflammatory reactions at and around the sites of intramus cular injection and (4) with oral administration labial perioral and oral reactions and/or gastrointestinal upsets and dermatitis and/or pruritus of anal and perianal area

DIAGNOSIS

PATCH TESTS—*Indications*—*(a)* Patch tests are generally of some value in differentiating between eczematous contact type aller gic dermatitis and atopic dermatitis or other eczematoid eruptions Positive reactions to patch tests somewhat favor a diagnosis of con tact type allergic dermatitis and negative results are somewhat against this diagnosis

(b) Patch tests are often of great value in the search for eliciting agents in acute and subacute contact type allergic eczematous derma titis In many such cases these tests are imperative and are an irre placeable means of achieving a satisfactory solution

Other forms of skin tests have not proved of value here

Materials—The discovery and the selection of suspected contact type allergenic materials depend on the physician s knowledge of the many substances which have been generally recognized as potential eczema togenic allergens and on his acquaintance with the variety of forms and the many situations in which exposures to such allergens are likely to occur The materials which are suspects in a particular case are then selected on the basis of history clinical picture course and localization of the eruption.

A Selection Based on History The following questions corre spond in great measure to those in the general suggestions for history taking in allergic dermatoses However these are of particular value in selecting materials for patch tests in cases of eczematous contact type dermatitis

1 What new exposures were encountered in the two or three weeks preceding onset of eruption? Within 24 hours preceding onset? *(a)* At work? *(b)* In hobbies or games? *(c)* At home or in garden etc—paints varnishes dyes cleansers insect or moth repellents flowers plants fertilizers etc? *(d)* As medicines including all used externally or taken or administered—e g nasal sprays eye drops creams lotions liniments *tinctures powders bandages dressings applied and remedies given* by mouth or injection? *(e)* In the form of clothing—dresses suits under wear nightwear socks shoes gloves furs handbags belts garters wrist watch straps jewelry ornaments etc? *(f)* As cosmetics including all forms of make up—creams rouges powders perfumes lipsticks nail polishes hair tonics hair lacquers hair straighteners wave sets pins combs dyes freckle removers wrinkle removers cleansers skin foods skin fresheners lash and eyebrow make up hand lotions soaps bath oils etc?

2 Which materials of the foregoing lists have been used habitually? Do you recall whether the eruption either began or got worse within several hours to a day or so after an exposure to any of these materials? Are there any materials which you had not used for some time and had resumed their use shortly before the onset or exacerbation of the eruption?

3 What new materials have been introduced into your environment by others? New soaps or insecticides at office workshop or home? New

furnishings at home or place of work—drapes carpets bedding etc.? A new paint job? Or lacquer? Or floor polish? New plants flowers decorative articles laundry agents etc.? New industrial processes and materials? New cosmetics shaving materials etc., of companions or associates? Of husband or boy friends? Of wife or girl friends? New pets? Or materials used on pets—flea powders mange cures soaps etc.?

4 What remedies have you used *on* or *for* this particular skin trouble? What external treatment agents were applied—salves lotions poultices dressings plasters tinctures etc? (Include those prescribed and those selected for self medication.)

5 Can you describe how the eruption felt and looked before any applications or medication? And what happened after the application of each particular agent? What remedies have you taken internally for this skin trouble? And what remedies have you received by injection or in other ways? And how did each affect the eruption?

The categories of such questions and the examples given do not purport to be complete or sufficient But together with the lists on page 249 they represent guides to the manner and direction of interrogation and they may aid the physician in taking a sharply focused history

B Selection Based on Clinical Picture The morphology of the eruption will sometimes suggest possible eliciting agents

Thus the linear distribution of papules and vesicles on exposed parts will suggest a plant allergen the discoloration of the skin a dye or other staining material edema of eyelids and orbit a hand borne or air borne allergen (nail polish, volatile agents dusts etc) well developed lichenification, pigmentation and thickening, a chronic allergenic exposure the presence of large clear vesicles or bullae and great swelling a violent acute exposure to a very potent allergen etc

C Selection Based on Course of Eruption Here the chronologic relationships between particular exposures and the onsets of exacerbations of eruptions are used as guides Similarly the time relationships between cessation or interruption of exposures and improvement of the dermatosis may serve as indicators

For example the patient is told to stop certain activities or to avoid certain types of exposures Then if the eruption improves the allergens of the particular activities and exposures are selected for patch testing Conversely the patient in a period of partial or total remission is told to expose himself deliberately to the allergens of certain activities or exposures Then if recurrences or exacerbations of the dermatitis appear these allergens are selected for patch testing

D Selection Based on Localization of Eruption In many cases the sites of origin or of greatest intensity of the eruption and the direction of its spread often provide most valuable clues to possible eliciting allergens Here again a knowledge of the eczematogenic allergens the various ways in which they are most likely to be en countered and the sites each will be inclined to favor is essential Table 20 which is not intended to be complete indicates some of the favored localizations of common forms of contact type derma titis and the manner in which the localization can give clues to materials to be selected for testing

Application of Tests —The allergenic materials selected for test ing must be prepared in such manner and in such concentrations and vehicles as to exclude their action as primary irritants[5] (toxic [6] action) and to obviate their other capacities to damage either locally or systemically

Liquids emulsions salves etc or semisolid materials are applied to the skin on small white linen or cotton squares (⅛–¼ in square) covered with impermeable material and held in place with adhesive (p 11)

Materials which can be powdered filed or shredded may be dusted or distributed on the linen or cotton squares (slightly moistened with water saline or sweat) which are then applied to the skin and

A primary irritant is defined as an agent which in a given concentration and vehicle and under given conditions of application *regularly* produces clini cally manifest *irritation without a preceding sensitization* of the skin

Toxic is in our opinion a poor word to designate this locally irritative or primary irritant effect. In immunologic discussions toxic should be used *only* when referring to the true toxins of micro-organisms and their effects

TABLE 20—CHARACTERISTIC SITES AND COMMON CAUSES OF ECZEMATOUS CONTACT TYPE DERMATITIS

LOCALIZATION	SUGGESTED CAUSES
1 Scalp and fore head	Scalp lotions tonics pomades etc. caps hats and their bands linings hair pins and other materials permanent wave solutions hair lacquers hair dyes etc.
2 Eyelids (one of the most sensitive areas)	Numerous substances used on scalp face and hands (soaps shaving lotions creams pow der nail lacquers and polishes etc.) Air borne volatile agents and dusts (plants pollens danders feathers insect sprays gaseous substances nasal sprays cleaning fluids antimoth preparations perfumes benzene dusts from clothing, bedding, fur niture materials of dyed clothing fabrics furs gloves etc.) Hair lacquers hats newsprint, rotogravure eyelash curlers
3 Face in general	Numerous materials transferred by hands or air borne (see preceding list) All substances used on or near face scalp or hands (cosmetics shaving soaps after-shaving lo tions gas masks nail lacquers gloves sponges used for application of make-up etc.)
4 Ears and retroau ricular areas	Scalp lotions salves hair lacquers and other materials applied to the scalp spectacles goggles perfumes scarves collars ear muffs telephone receivers etc.
5 Nose and nasolabial areas	Nose drops nasal ointments sprays handker chiefs paper tissues etc.
6 Lips and perioral areas	Lipsticks pomades mouthwashes tooth pastes and powders materials of dental origin dental floss tooth brush plastics and bristles Sometimes certain foods (oranges other citrus fruits and their juices)
7 Neck—front, sides and/or back	Nail polish and lacquers perfumes hair lac quers and dyes collars scarves neckties clothing fabrics (wool other fabrics finishes and dyes etc.) Substances used on scalp necklaces jewelry flowers attached to dress

Based o tables n Sulzberger M. B d Wolf J *Dermat log Therapy in General P actic* (2d ed. Chicago The Yea Book Publishers Inc. 1942) and Pillsbury, D M. Sulzberge M B and Livingood C. S *Manual of Dermat l gy* (Ph lad lphia W B S unders Company 1942)

The scalp is often remarkably resistant to extern l irritants and allergens. Thus, dermatitis caused by substances used on th scalp often ppears not p im rily on th scalp but predom antly o ex lus vely on other more sens tiv sk areas such as th eyelids ears and retroaur cular reas, o pe nd other parts of th neck, the face gen ral and even th hands.

TABLE 20 CONTINUED—CHARACTERISTIC SITES AND COMMON CAUSES OF ECZEMATOUS CONTACT TYPE DERMATITIS

LOCALIZATION	SUGGESTED CAUSES
8 Sides of neck upper chest wrists cubital spaces inner and anterior aspects of thighs ankles lower legs and dorsa of feet	Typical of clothing materials and their finishes and dyes in military services uniform or wool dermatitis
9 Hands forearms and face	An almost infinite variety of substances too numerous to list Most occupational and industrial excitants including soaps and cleansers Substances encountered in military activities plants (ivy etc) gasoline greases paints chemicals gloves steering wheels instruments or substances encountered in hobbies or games topical medicaments applied to self or to others all objects which may be touched handled held or worn
10 Trunk—various sites	Clothing plants underwear night clothes sweaters bathing materials soaps materials used for massage and slenderizing procedures sun tan lotion creams
11 Perianal	*Feces and decomposition products* (lack of cleanliness e g thorough washing after defecation use of toilet paper etc) intestinal parasites fungi and other micro-organisms ingested foods (fruits oils) substances in enemas suppositories topical medicaments underdrawers toilet paper etc materials used on vulva or in vagina
12 Penis and scrotum	Substances carried by the hands plants clothing medicaments used for pediculosis chemical prophylaxis fungous infections etc condoms (rubber) medicated douches anticonceptional agents (used by partner) etc Fabrics finishes and dyes in underdrawers shorts pajamas etc rubber and elastic supporters
13 Thighs legs and ankles	Dyed materials and materials of trousers underdrawers socks etc match boxes cigaret lighters coins and other metallic objects carried in trouser pockets etc. Volatile and air borne substances dusts inside trousers metal objects fluid in lighters etc Plants lacquers on toilet seats garters

TABLE 20 CONTINUED—CHARACTERISTIC SITES AND COMMON CAUSES OF ECZEMATOUS CONTACT TYPE DERMATITIS

LOCALIZATION	SUGGESTED CAUSES
14 Lower portions of legs and feet	Shoes socks stockings (leather dyes tanning agents dyes and finishes of fabrics etc) plants
15 Feet (particularly dorsa of great toes) sides and dorsa of feet and sometimes soles (often with little or no interdigital involvement in contrast to fungous infections)	Shoes leather dyes tanning agents shoe polishes sock dyes and finishes rubbers foot powders fungicides medicaments used to prevent or to treat "athlete s foot etc.
16 More or less generalized eruptions	Any of the aforementioned agents may produce not only localized but generalized eczematous dermatitis Also medicaments applied to numerous or widespread areas and eczematogenous medicaments taken by mouth or injected (arsenicals mercurials quinine salicylates hexamethylenetetramine sulfonamides penicillin etc.)

covered and fixed in the usual manner Materials which themselves consist of tissues (clothing leather cloth etc) are cut into small squares or pieces and are moistened and applied like the linen or cotton patches

In the case of many simple chemicals or mixtures the safe and suitable vehicles and concentrations for patch testing have been established by careful assays Table 21 lists the results of assays for a variety of substances

Allergenic oils (in acetone) from a great number of plants are prepared for patch testing and can be obtained from the Graham Laboratories Dallas

Readings are made and recorded at 48 hours and later (p 12) The results of patch testing with these substances are evaluated as described on page 14

TABLE 21 —SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Acetanilid	pdr as is	
Acetic acid	3	aq
Acetone	as is	
Acetphenetidin	pdr as is	
¶Acridine	pdr pure	
Agerite Alba (prop)	75	pet.
Agerite Alba (prop)	20	alc
Alcohol denatured (controls)	as is	
Alcohol U S P	70-95	
Aldehyde amines	as is	
Alizarin	pure	
†Alizarin 778	1	alc
Alizarin red 1034	pdr as is	
Alizarin sulfate	10	aq
Alkaloids—as salts	1	aq
Allspice	as is	
Almond oil	as is	
Alpha naphthylamine	pure	
Alum	10	aq
Aluminum acetate	10	aq
Aluminum chloride	2	aq
Aluminum scrapings	as is	
Alypin	1	aq
Amber oil of	1	alc
Amido-azobenzol	2–10	o o
Amido-azotoluene hydrochloride	1	aq
Amidol	5	aq
Amidophenol (ortho- meta or para)	2–10	pet

Based on tables in Rostenberg A. J nd Sulzbe ger M B J I vest. Dermat. 2 93 1939 nd S l be g r M B and Baer R L *1943 Y ar B ok of Dermatol gy and Syph l l gy* (Ch cago The Year Book Publi h rs Inc)

K y to Abb eviati s and Symbols

cet.	=	aceto	Ger	=	G rman
lc	=	alcohol 70 pe c t	o o	=	olive oil
aq	=	aq eous	pdr	=	powd r
chlor	=	chloroform	pet	=	petrolatum
c.o	=	casto o l	prop	=	propr etary prep rat on
controls	=	perform co trol tests on normal ind duals	s	=	saturated
			sol.	=	solu ion
dext.	=	15 pe cent dext n sol t on			

† Our tests w th th s p rt cul b tance have been less tha 20 i number

‡ Our tests w th th p cul substa ce h ve been less than 20 n mber and we suspect th t the concentration g ven may be too strong fo routine testing.

We suspect th t the concentration g en is too trong for rout ne testing.

¶ This substance m y photosen tize the patch test s es I e after th patch has been removed and on exposure to light, dermatit s may supervene

§ This substance has been known to cause a sens tization of the eczematous type even after a s ngle application to normal skin

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Amines	2	pet.
Amino-azotoluene	2	alc
Amino-azotoluene	pdr as is	
Aminodracylic acid	1	alc
Aminopyrine	as is	
Ammonia	1–2	aq
Ammonium bichromate	0 5	aq
Ammonium bichromate	0 5	pet
Ammonium carbonate	15	aq
Ammonium chloride	3	aq
Ammonium fluoride	0 5–2	aq
Ammonium nitrate	10	aq
Ammonium persulfate	1–5	aq
Ammonium sulfate	10	aq
Amyl acetate	pure	
Analgesics	as is	
Anesthesin	5	pet
Aniline	10–25	o o
Aniline black 870	pdr pure	
†Aniline brilliant green	pdr pure	
Aniline dyes	2	o o
Aniline dyes	2	pet
Aniline dyes	pdr pure	
Anise seed oil	25	c o
Anthracene	pure	
†Anthral n (1–8 dihydroxyanthranol)	0 1	pet
Anthraquinone	pdr pure	
Anthraquinone blue S R. 1089	pure	
Anthrarobin	3	pet
Anticorrosion oils (controls)	as is	
Antihidrotic (prop) (controls)	as is	
Antimony chloride	2	aq
Antimony oxide	pure	
Antipyrine	as is	
Aquaphor (prop)	as is	
†Aqua Velva (prop)	as is	
Argyrol	10	aq
Arnica tincture of	20–25	pet
Arnica tincture of	20–25	alc
Arning's tincture modified (anthrarobin tumen ol ammonium glycerin spirits ether)	as is	
Aromatic o ls	1	alc
Arsenious trioxide	pdr pure	
Asphalt (no adhes ve covering)	as is	
Aspirin	as is	

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Atabrine	as is	
Atropine sulfate	1	aq
Auto lubricating oils	60	o o
Auto polishes (controls)	as is	
Azochloramid	0 2	triacetin
Bakelite (scrapings)	as is	
Baking powder	as is	
Baking soda	as is	
BAL (2–3 dithiopropanol)	as is	
BAL *ointment (or in ethylene glycol)*	5	
Balata (rubber)	as is	
Balsam of Peru	10	pet
Banana peel oil	pure	
Barbiturates	as is	
Barium hydrate	0 5	aq
Barium sulfate	as is	
Barley oil	pure	
Bayberry oil of	25	c.o
Bayberry oil of	25	pet.
Beef fat oil	pure	
†Beef salt	5	aq
Beeswax	pure	
Beetle (prop)	pure	
Benzaldehyde	10	aq
Benzanthrone	pure	
Benzidine	pure	
Benzine	60	o o
Benzocaine	5	pet.
Benzoic acid	6	pet.
Benzoic anhydride	10	aq
Benzol	*60*	o o
Benzoquinone	1	aq
Benzoyl amino-metoxychlor anthraquinone	2	o o
Benzyl alcohol	10	pet.
Benzyl benzoate	*10*	*aq*
Benzyl chloride	5	aq
Benzyl cinnamate	10	pet
†Bergamot oil of	10	pet
Betahydroxy anthraquinone	1	alc
Betanaphthol	10	o o
Beta phenylacrylic acid	5	pet
Bismarck brown 331	pure	
Bismogenol	as is	
Bismuth colloidal solution	as is	
Bismuth metallic (scrapings)	as is	
Bismuth oxychloride	5	pet.

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Bismuth subnitrate	25	pet.
Bismuth subsalicylate	14	o o
Black Flag (prop)	pdr as is	
Black Flag (prop)	liquid 25	o o
Black rouge	as is	
Bleaching powder (controls)	10	aq
Blueing	as is	
Borax	sat. sol	
Boric acid	pdr pure	
Boric acid ointment USP	as is	
Borocaine	1	aq
‡Brake Fluid (prop) (controls)	as is	
Brass metallic scrapings	as is	
Brass polish	10	aq
Brass weldings scrapings	as is	
Brazil nut	as is	
Brazil wood (redwood)	as is	
†Brilliant cresyl blue BB(L) 877	pure	
Brillo (prop)	as is	
‡Bromo acid 768	pure	
†Bronze liquid paint	as is	
Burow's solution	10	aq
Butes n	1	alc
Butesin picrate ointment (prop)	as is	
Butyl acetate	pure	
Butyl alcohol	pure	
Butyric acid	1	aq
†Cade oil of	5–10	pet
†Cadmium orange	pure	
†Cadmium red deep	pure	
†Cadmium red light	pure	
Caffeine	1	aq
Calcimine	as is	
Calcium arsenate	pdr pure	
Calcium carbonate	3	aq
Calcium chloride	2–10	aq
*Calcium cyanamide (crude)	10	aq
Calcium fluoride	0.5	aq
Calcium hydrate	0.125	aq
Calcium nitrate	10	aq
Calcium oxide	10	aq
Calcium phosphate	10	aq
Calcium sulfide	1	aq
Calmitol ointment (prop)	as is	
Calomel	pdr pure	
Camomile oil of	25	o o

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Camomile oil of	25	pet.
Camphor	pdr pure	
†Camphor ice (prop)	as is	
Camphor oil of	10	pet
†Camphor spirits of	as is	
Canada balsam	as is	
Cantharides tincture of	1	alc.
Capsicum tincture of	1	alc.
Caraway seed oil of	25	c.o
Caraway seed oil of	1	alc.
Carbazole	pdr pure	
Carbon	as is	
Carbon disulfide	60	o o
Carbon paper	as is	
Carbon tetrachloride	pure	
Carborundum	as is	
Cardamon	as is	
Cashew nut shell oil	3–5	alc.
Cassia oil of	1	alc.
Cauline (prop)	as is	
Cement (controls)	as is	
Ceresin	pure	
Charcoal	as is	
Chestnut extract of	10	aq
Chicken fat oil	pure	
Chloral hydrate	10	aq
Chloramine	0 5–1	aq
Chlorbenzene	5	o o
Chloretone	2	alc.
Chlorinated lime	2–10	aq
Chlorinated naphthalene	pure	
Chloroform	40	o o
Chocolate	as is	
Chrome alum	as is	
Chromic acid	0 5–1	aq
Chromium chloride	2	aq
Chromium potassium sulfate	10	aq
Chromium sulfate	2	aq
Chrome yellow	pdr pure	
Chrysarobin	1–5	pet.
Chrysoidin brown	pdr pure	
Cinnabar	3	pet.
Cinnamic acid	5	pet.
Cinnamon	pdr as is	
Cinnamon oil of	5	o o
Cinnamylic acid	5	pet.

TABLE 21 CONTINUED—SUBSTANCES, CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

		%	VEHICLE
Citric acid		1	aq
Citronella		as is	
Cleaning fluids inflammable (prop) (controls)		60	o o
Cleaning fluids noninflammable (prop) (controls)		as is	
Clorox (prop)		10	aq
Clothing and clothing materials		as is	
Cloves	pdr	as is	
Cloves oil of		25	c.o
Cloves oil of		1	alc
CN (prop)		1–10	aq
*Coal tar crude		5–10	pet
Cobalt chloride		2	aq
Cobalt oxide		pure	
Cocaine		1	aq
Cochineal natural 932		10	aq
Cocoa		as is	
Coconut oil of		pure	
Codeine sulfate		1	aq
Cod fish oil		pure	
Cod liver oil		as is	
Coffee		pure	
Coffee oil of		pure	
Collodion		as is	
Colza oil		as is	
Copal		pure	
Copper chloride		1	aq
Copper cyanide	pdr	pure	
Copper scrapings		as is	
Copper sulfate		5	aq
Coriander oil of		1	alc
Cosmetics (controls with hair tonics etc cuticle softeners etc are usually primary irritants)		as is	
Cotton seed oil		pure	
Crayons		as is	
Creosote		10	o o
Cresol		0 5–1	aq
Crude oil		as is	
Crystal violet 681		2	aq
Cumaron		pure	
Cutch		pure	
‡Cuticle remover (controls)		as is	
Cutting oils (controls)		as is	
Cyclohexanol		50	o o
Damar (resin)		pure	
DDT (dichlordiphenyltrichlorethane)		5	acet

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Decahydronaphthalene (dekalin)	50	o o
Dekalin (Ger prop name for a turpentine substitute)	50	o o
Denatured alcohol (controls)	as is	
Deodorants	as is	
Depilatories (controls)	as is	
Dermatol (Ger prop dusting powder)	pure	
Dextrin	50–80	aq
Diacetylamidoazotoluol	2	pet.
Dianisidine	pure	
Diazonium salts	1	pet.
(Sym) Di beta naphthyl paraphenylene-diamine	pure	
§Dichlorbenzene	5	chlor
Dichlorbenzidine	5	alc.
Dichloronite benzine	10	aq
Diethylanius—ethanol	1	aq
Diethylene glycol	10	aq
Dimethyl amine	pure	
Dimethyl aniline	10–25	o o
1–2–4 dichloronitrobenzene	1	acet.
1–4–2 dichloronitrobenzene	1	acet.
1–8 dihydroxy-anthranol	0 1	pet.
1–2 dihydroxy-anthraquinone	0 5	alc.
1–8 dihydroxy anthraquinone	0 5	alc.
1–4 dihydroxy-anthraquinone	0 5	alc.
§1–2–4 dinitrochlorbenzene	1	acet.
Dinitrocresol	5	chlor
2–4 dinitrophenol	10	aq
Dinitrotoluol	sat.	alc.
Di-orthotolyl guanidine	pdr pure	
Di-orthotolylthio-urea	pdr pure	
Diphenyl	pure	
Diphenyl guanidine	2–10	o o
Dithio acids salts of	pure	
Ditolyl amines	pure	
Dragon s Blood (prop)	as is	
Dural	as is	
Dusts	as is	
Dust oil	as is	
Dutch Cleanser (prop)	as is	
Dyes lakes and toners	pdr pure	
Earthy pigments	pure	
"El Key" Insecticides (prop)	50	o.o
Elon fresa (prop)	0 5	aq
Emetine hydrochloride	pdr pure	

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Enamel (controls)	as is	
Eosin pdr	as is	
Ephedrine	1	o o
Erythrosine	as is	
Esbach s reagent	2	aq
Essential oils (controls)	1	alc
Esters	pure	
Ester gums	pure	
†Ether	60	o o
Ethyl acetate	pure	
Ethylaminobenzoate	5	pet.
Ethylene d chloride	50	o o
Ethylene dichloride	0 1	alc.
Ethyl mercury chloride	0 5	aq
Ethyl mercury phosphate	0 5	aq
Eucalyptus oil of	1	alc.
Eye lotions cosmetics shadows	as is	
Fagi oil of	5	pet
Fenchyl alcohol	pure	
Fennel oil of	1	alc
Ferric chloride	2	aq
Ferric ferrocyanide	as is	
Ferric sesquichloride	10	aq
Ferrosulfate	10	aq
Fertilizers most commercial preparations (controls)	as is	
Fixatif	as is	
Flavoring oils (controls)	2	alc.
Flit (prop)	25	o o
Floor wax (controls)	10	o o
Flour all kinds	as is	
Flour bleaches (controls)	as is	
Flowers fresh dry artificial (controls)	as is	
†Fluorene	pure	
Fluorescein	1	alc.
Flux aluminum	as is	
Flux iron	as is	
Flycide (prop)	25	o o
Foods any kind (except rinds of certain fruits spices mustard etc)	as is	
Formaldehyde	5	aq
Formic acid	1	aq
Fowler s solution	as is	
Frostilla (prop)	as is	
Fruit, citrus peel (controls)	as is	

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Hydroterpens	50	o.o
Hydroxymercurichlorphenol	0 5	aq
Hydroxymercuricresol	0 5	aq
Hydroxymercurinitrophenol	0 5	aq
Hypnotics	as is	
Ichthyol	5–10	pet.
Indigo	10	aq
†Indole	sat.	aq
Inecto A (prop hair dye)	as is	
Inecto B (prop hair dye)	as is	
Ink eradicators (controls)	as is	
Inks	as is	
Iodine crystals	0 5	pet.
Iodine crystals	1	alc.
Iodine tincture of U S P (Do not cover! Simply paint on)	as is	
†Iodobismitol (prop)	as is	
Iodoform	25	pet.
†Iridium chloride	10	aq
Iron chloride	2	aq
Iron metallic scrapings	as is	
Iron sulfate	10	aq
Istizin 1-8 dihydroxyanthraquinone	0 5	alc.
Javelle water	10–20	aq
J O Roach Powder (prop insecticide)	as is	
Juniper oil of	25	c o
Juniper oil of	1	alc
Kaini (Ger prop fertilizer)	10	aq
Karbolinium (Ger prop wood preservative)	50	o o
Kill It (prop insecticide)	as is	
Kerosene	60	o o
Lac dyes	50	pet.
Lacquers (controls)	as is	
Lakes	50	o o
†Laketine pdr	as is	
Lanolin	as is	
Lard	as is	
Larocaine	1	aq
Larvex (prop)	10	o o
Latex	as is	
Laurel oil of	25	c.o
Lavender oil of	1	alc.
Lead arsenate	pure	
Lead arsenate	5	aq
Lead azide	pure	

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Lead chloride	pure	
*Lead red	as is	
Lead styphnate	pure	
Lead subacetate	0 2	aq
†Lead ulfide	2	aq
Lead white	as is	
Leathers natural tanned dyed imitation	as is	
Lemon oil of (controls)	1	alc
Licorice	as is	
Lime burnt	10	aq
Lime slaked (controls)	as is	
Linalool	1	alc
Linseed oil	as is	
¶Lipstick	as is	
¶Liquor carbonis detergens	10	pet
Liquor sesquichlorati	10	aq
Listerine (prop)	10	aq
Lithol red 189 as lakes and toners	as is	
Logwood	sat	aq
Lubricating oils (controls)	as is	
Lugol s solution U S P	50	aq
Luminal (prop)	as is	
Lysol (prop)	1	aq
Mace oil of	1	alc
Machine oil (controls)	50	o o
Manganese oxide	pure	
Maroon 677 (partly impure magenta)	as is	
Mascara	as is	
Mastic	pure	
Mastisol (Ger prop collodion like substance)	as is	
Melissa oil of	1	alc.
Menthol	1	pet.
†Mentholatum (prop)	as is	
Mercaptens	pure	
Mercurochrome	2	aq
Mercury bichloride	0 1	aq
Mercury fulminate	pure	
Mercury oxycyanate	0 1–0.2	aq
Mercury white ammoniated	5–10	pet
Mercury yellow oxide of	5	pet
Merthiolate tincture of (prop)	as is	
Mesquite wood	as is	
Metals pure alloys	as is	
Metaphen	0 5	alc
Metatoluylene diamine	pure	

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Methyl acetate	pure	
Methyl alcohol	pure	
Methyl aniline	10–25	o o
Methyl benzoate	1	aq
Methyl heptin carbonate	0 1	alc.
Methyl orange 142	5	aq
Methylprotocatechuic aldehyde	10	pet
§†Methyl salicylate	2	o o
Methyl violet 680	2	aq
Methyl violet, as lake	as is	
Metol (prop)	5	aq
Michler s hydrol	5	alc.
Mineral colors or pigments	as is	
Mineral oil	as is	
Mint	as is	
Mirbane oil	25	c o
†Mistol (prop)	as is	
Monobenzyl para-amino-phenol	pure	
Monochlor benzene	5	o o
Morphine	1	aq
Moth flakes	as is	
Mouth washes	as is	
Mucilage	as is	
Mustard oil of	1	alc
Naftalan (Ger prop)	10	pet
Nail polish	as is	
Naphtha	50	o o
Naphthalic acid	1 5	aq
Naphthalene	pure	
2 Naphthalene 1-sulfonic acid azo-beta naphthol	as is	pdr
Naphthenol	50	o o
Naphthol yellow	pure	
Naphthylamine	2	alc.
Neoarsphenamine	1	aq
Nickel nitrate	5	aq
Nickel sulfate	5–10	aq
N cotine salicylate	5	aq
Nigrosine	pure	
Nile blue	pure	
Nitric acid	2–3	aq
Nitrobenzol	10–25	o o
Nitrophenol	5	chlor
§Nitroso-d methyl an l ne	1	alc.
Novoca ne (prop)	2	aq
†Noxon (prop)	as is	

Do ot test w th bas

TABLE 21 CONTINUED — SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Nupercaine (prop)	1	pet
Nutgalls roasted	as is	
Nutmeg oil of	25	c.o
Nylander s reagent	as is	
Nylon	as is	
Oakum	as is	
Oat oil	as is	
Ochre red	pure	
Oidiomycins (controls)	undil	
Oil of bitter almonds	1	alc
Oil paints in tubes	as is	
Oil paints for walls	50	o o
Olibanum	pure	
Olive oil	pure	
Orange II 151 as lake	pure	
Orange oil of	1	alc.
Orange oil of	25	c o
Orris root powder	pure	
§Orthoform	25	pet
Orthonitranisol	5	aq
†Osmic acid	10	aq
Oxalic acid	5	aq
Paint house (controls)	50	o o
†Palladium chloride	10	aq
Palm oil	as is	
Panthesine	1	aq
Para-amidophenol	3	aq
Para-amidophenol	10	o o
Para aminodiphenyl amine	3	aq
Para aminophenol	10	pet
Para-di-chromo benzine	10	aq
Paraffin	pure	
Paranitro benzoic acid	pure	
Paranitrochlor benzene	10	acet.
§Paranitroso-dimethylaniline	1	acet.
Paraphenylendiamine	2	pet
Para red, deep-44 as lake or toner	as is	
Para red light-44 as lake or toner	as is	
Pastes	as is	
Peanut oil	as is	
Pellidol (prop)	2	pet.
Penicillin	pdr as is	
Penicillin ointment 500 units per Gm	as is	
Penicillin (prop topical remedies) (Keep in icebox!)	as is	

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Peppermint oil of	25	c o
Peppermint oil of	1	alc.
‡Perfumes (controls)	as is	
‡Perfume oils (controls)	1	alc
Peroxide U S P	as is	
Persil (Ger prop cleansing substance)	10	aq
Peterman s Insecticide (prop)	25	o o
Petrolatum white or yellow	pure	
Petroleum	20	o o
Phenacetin	as is	
‡Phenanthrene	pdr pure	
Phenolphthalein white or yellow	pdr as is	
Phenolphthalein white or yellow	pdr 2	alc
Phenyl-alpha naphthylamine	pure	
Phenyl beta naphthylamine	pure	
Phenyl glycine	pure	
Phosphorus trisulfide	0 5	pet.
Photographic developers	5	aq
Phthalic acid	1–5	aq
§†Phthalic anhydride	1	alc
Picric acid	1–5	aq
§Picryl chloride	1	acet
Pigments for artists etc	as is	
Pine oil (controls)	pure	
‡Pitch (just apply) (no covering)	as is	
§Plants fresh dry any part of (controls)	as is	
Plant oils (commercial preparations for testing are available)	as made	
Plaskon	pure	
Plaster of paris	as is	
Plaster wall	as is	
Plastics	as is	
†Platinum chloride	10	aq
§Poison ivy extract—8% solids	0 1	acet
Polishes commerc al (prop)	as is	
Pontachrome blue black R 202	pure	
Pontacyl black (similar to 246)	pure	
Pontamine black 581	pure	
Pontamine blue-406	pure	
Pontamine diazo black 401	pure	
Pontamine fast orange S	pure	
Pontocaine hydrochloride	2	o o
Poppy seed oil	as is	
Potash	10	aq

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Potassium acetate	10	aq
Potassium arsenite USP	as is	
Potassium bichromate	0 5–1	aq
Potassium bromate	6	aq
Potassium bromide	1–6	aq
Potassium bromide	25	pet
Potassium carbonate	0 7–3	aq
Potassium chlorate	10	aq
Potassium chloride	3–10	aq
Potassium chromate	0 5	aq
Potassium citrate	10	aq
Potassium ferricyanide	10	aq
Potassium ferrocyanide	10	aq
Potassium hydroxide	0 5	aq
Potassium iodide	3–6	aq
Potassium iodide	25	pet
Potassium nitrate	25	aq
Potassium permanganate	1	aq
Potassium persulfate (should be freshly made)	2 5	aq
†Potassium salicylate	as is	
Powder cleansing scouring (controls)	as is	
Powder face bath	as is	
ʳPragmasul Oint (prop)	as is	
ʃPragmatar Oint (prop)	as is	
§Primrose expressed juice of fresh plant	25	aq
§Primrose leaf	as is	
Procaine (base)	1	o o
Procaine hydrochloride	1	o o
Propyl ne glycol	10	aq
Protein extracts foods plants bacteria	as is	
Pyredine	30	o o
Pyrethrum milled powder	as is	
Pyrethrum tincture of	as is	
†Pyro	as is	
Pyrogallol	3	aq
Qualatum (prop)	as is	
Quercitron	pure	
ʳQuinine	1	aq
ʳQuinine sulfate	25	pet
Quinizarin	0 5	alc
Quinosol	0 2–0 5	dext
Rapeseed oil	pure	
Rapidol (prop)	as is	
Raw umber	as is	
Red moss	as is	

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
§Res ns (controls see plants")	as is	
Resorcin (controls)	3	aq
Rhodamine B 749 lakes and toners of	as is	
†Rhodium chloride	10	aq
Rice oil	as is	
Rockwood	as is	
Rose o l of	25	pet
Rose oil of	1	alc
Roux	as is	
Rubber rubber products	as is	
Rubber (synthetic)	as is	
†Rusci oil of	6	pet
Rye oil of	pure	
Safranine O 841	pure	
Sagrotan (Ger prop disinfectant)	1	aq
Sal ammoniac	3	aq
Sal cylic acid	5–10	pet
Salol	as is	
Salves (prop) (controls)	as is	
Sangajol (Ger prop name for a turpentine substitute)	30	o o
Santal oil of	1	alc
Sassafras o l of	2	o o
Sassafras o l of	1	alc
Scalp lotions (controls)	as is	
Scopolamine	1	aq
Sensol	as is	
Shampoos (controls)	as is	
Shellac (controls)	as is	
Shoe dyes (controls)	50	o o
Shoe polishes (controls)	60	pet
Sidol (Ger prop silver polish)	10	aq
Silver amalgams	as s	
Silver metallic scrapings	as is	
Silver n trate	5	aq
Silver nucleinate	5	aq
Silver paint	as is	
S monizer (prop)	as is	
Skatol	sat	aq
Smokeless gunpowder	as is	
Soaps (controls)	1–3	aq
Soap tincture of green	5	pet
Soap tincture of g een	2 5	alc
Sod um arsenate	10	aq
Sodium benzoate	₋0	aq

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Sodium bicarbonate	8 3	aq
Sodium bichromate	3	aq
Sodium bromide	25	pet
Sodium carbonate	3–10	aq
Sodium chloride	10	aq
Sodium fluoride	0 5	aq
Sodium fluorosilicate	0 5	aq
Sodium hydroxide	0 5	aq
Sodium hypochlorite	10	aq
Sodium hyposulfite	1	aq
Sodium meta aminobenzoate	1	aq
Sodium metasilicate	2	aq
Sodium oleate	1	aq
Sodium para aminobenzoate	1	aq
†Sodium salicylate	1	aq
Sodium stearate	1	aq
Sodium sulfate	5	aq
Sodium sulfide	2	aq
Sodium sulfite	1	aq
Sodium thiosulfate	5	aq
Soluble blue 325	pure	
Spearmint oil of	1	alc
†Spermaceti	pure	
Spirits of ether	as is	
Spring spray (auto) (controls)	as is	
Stains	as is	
Starch	as is	
Stearic acid	1	aq
Steel wool	as is	
Sudan III 223	5	o o
Sugar	as is	
†Sulfarsphenamine	3	aq
Sulfogene carbon	pure	
Sulfogene golden brown	pure	
†Sulfonamides	pdr as is	
†Sulfonamides (in cold cream)	5	
†Sulfonamides (prop topical remedies)	as is	
Sulfonated oils	pure	
Sulfosalicylic acid	pure	
Sulfur (precip or sublimed)	5–10	pet.
Sulfur monochloride	1	CS_2
Sulfuric acid	5	aq
Sulfurous acid	1–2	aq
Sumac leaves fresh or dry	as is	
Sunflowers oil of	as is	

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Tallow	as is	
Tannic acid	1	aq
¶Tar paper	as is	
¶Tar solution of N F	10	aq
¶Tars (No covering! Simply apply)	as is	
Tartar emetic	3	aq
Tartar emetic powder	as is	
Tartrazine yellow-640	pure	
Terp neol	pure	
Tetrachlornaphthalin	50	o o
Tetralin (tetrahydronaphthaline)	30	o o
Tetramethyl-diamino-benzophenone	5	alc
Tetramethyl thiuram-disulfide	pure	
Tetramethyl thiuram mono-disulfide	pure	
Tetryl	sat	ether
Thioureas	pure	
Thiuram sulfides	pure	
Thyme oil of	25	c.o
Thyme oil of	25	alc.
Thymol	1	pet
†Thymol iodide	25	pet.
†Tin chloride (stannous)	10	aq
Tin foil	as is	
Tincture veratrum viride U S P	as is	
Tintex (prop)	as is	
Tobacco extract (controls)	as is	aq
Tobacco leaf (controls)	as is	
Toilet waters	as is	
Toluidin	10–50	o o
Toluol	50	o o
Toners	pdr pure	
Tooth pastes powders	as is	
Tragacanth	1	aq
Triacetin	pure	
Trichlorethylene	50	o o
Trichlortoluol	50	o o
Trichophytins (controls)	und l	
Tri-ethanol am ne	1	aq
Tri n tro-anisol	0 01	chlor
1–2–4 trinitrobenzene	1	acet
1–3–5 trinitrobenzene	1	acet
Trinitrotoluol	sat	alc
Trisodium phosphate	2	aq
†Trypan blue 477	pure	
Trypan red 438	pure	

TABLE 21 CONTINUED—SUBSTANCES CONCENTRATIONS AND VEHICLES TO BE USED IN PATCH TESTING

	%	VEHICLE
Tryparsamide	6	aq
Tuberculins (controls)	undil	
Tumenol (prop)	5	pet
Tumenol ammonium (prop)	6	pet
Turmeric	pure	
Turpentine (controls)	50	o o
Tutocaine	2	aq
Typewriter ribbon	as is	
Tyrosine	sat	aq
Ultramarine blue	as is	
†Uranium chloride	10	aq
Urea	10	aq
Uric acid	1	aq
Vanilla oil of	25	alc.
Vanillin	10	pet
Varnish (controls)	as is	
†Varnolene	60	o o
†Venetian red	pure	
†Vert emeralde	pure	
Victoria blue	pure	
†Vinegar	as is	
Vinyl resins	pure	
Vioform (prop)	3	pet.
Walnut oil of	pure	
Water colors	as is	
Wax floor (controls)	50	o o
Waxes polishing in general (controls)	as is	
Wheat oil of	as is	
Whitfield s oint N F	as is	
Window sprays	as is	
§Wintergreen oil of	1	alc
Witch hazel	as is	
Woods natural painted stained (controls)	as is	
Wormwood oil of	25	c o
†Xeroform	25	pet.
Xylol	50	o o
Yellow olive	pure	
Zinc chloride	2	aq
Zinc chromate primer (after drying)	as is	
Zinc oxide	pure	
Zinc peroxide	pure	
Zinc stearate	pure	
Zinc sulfate	10	aq
Zinc white	as is	
Zonite (prop)	1	aq

DIAGNOSTIC ETIOLOGIC SIGNIFICANCE OF REACTIONS TO PATCH TESTS

The positive results of patch tests are of diagnostic and etiologic significance only when corroborated

1 By the exclusion of other causes
2 By the clinical findings
3 By the course including the beneficial effects of avoid ance or reduction of exposure to the allergens which produce the patch test reactions and the harmful effects of clinical re-exposures to these allergens

Contraindications and Dangers —Patch tests when used cor rectly constitute one of the safest means of clinical testing Neverthe less certain contraindications and dangers do exist and, like all skin tests *patch tests should never be applied without the necessary knowledge and the adequate indications*

The contraindications and dangers of patch testing are fully de scribed under common technics page 15 Though in part repeti tious because of their great importance the following *don ts* are inserted here

1 Don t test uselessly indiscriminately or in a haphazard manner Apply only the suspected allergens

2 Don t test patients with severe or widespread dermatoses during the acute or active period You may cause severe flare ups and prolong the course by days or weeks Moreover skin test results during the acute stages may be misleading Many patients will react nonspecifically" during the acute phase of their dermatitis and at that time react to substances to which they will not react when the eruption is quiescent.

3 Don t neglect the treatment while you are planning and executing the skin tests In order to shorten the course and reduce the risks of

aggravation and chronicity every patient must be treated at once and continuously until cured Correct treatment consists of all suitable general and local measures including x rays if indicated

4 Dont apply new or unknown substances unless you know they are safe otherwise you may create new sensitizations local damage beyond repair or even systemic poisoning by absorption Your results will be valueless unless you know what the substance does on normal skins (see Table 21) Moreover you may be held legally liable for ill effects from the application of substances about which you have insufficient data.

5 Dont apply skin tests to areas on which any severe or lasting reactions would be disfiguring (*face neck, arms decolleté areas* in women, legs in dancers etc.)

6 Dont think that the vehicle or base used is of no consequence The same substance in the same concentration in water or in acetone or in olive oil or in xylene etc. will produce entirely different reactions (Acetone will evaporate and leave a concentrated residue oil will hold the solution in contact with the skin xylene will degrease the skin and enhance penetration and will also evaporate etc.) Therefore all test substances must be standardized with due regard for their concentrations in the *particular* vehicle or vehicles to be used

7 Dont conclude that any form or manner of application will do Use only a standardized test procedure such as the classic patch test or some method that has been equally well studied and standardized for the particular agent and vehicle Painting a substance on without a covering letting a drop fall on the skin, applying the allergen as an inunction with or without a covering putting it on under semiocclusive conditions or under a completely occlusive dressing letting it impinge on the skin as a vapor—each such variation will exert different effects and may cause entirely different results For example all normal skins will tolerate a painting with official tincture of iodine or with turpentine or strong soap solutions but most *normal* skins will be *damaged* by these same materials put on under the semiocclusive patch test

8 Dont destroy the value of your tests by poor recording. When applying more than one test at one sitting, make a careful written record numbering all sites making a sketch of their arrangement and

noting the exact nature of the material applied to each skin site (Fig 5) Mark each site on the skin with indelible pencil or other long lasting marking agent, preferably with a number corresponding to that on the sketch, thus making it possible to identify the sites after several days

9 Don t misread the results Patch tests in eczematous dermatitis should reproduce some stage of an eczematous eruption, i.e redness or edema, papules papulovesicles vesicles or bullae or later lichenification, etc. (Abrasions or follicular reactions denudations or pustules or other noneczematous reactions are not usually to be regarded as having the same significance as eczematous responses.) Often a transitory erythema caused by removal of adhesive or redness and indentations caused by pressure by solids or particulate materials may be present after the test is removed Wait for these mechanical effects to subside before definitive reading In patients with pronounced sensitivity to adhesive the erythema may persist read the reaction of the central part only i.e that which has been under the patch, not that under the adhesive When there is a great hypersensitivity to adhesive tape tests must be secured to the skin with some adhesive tape substitute found to be nonirritating in the particular case (Frisket, rubber cement scotch tape gauze bandages etc)

10 Don t apply an agent or solution unless you know what it does to normal skins when used in the vehicle concentration and manner of application you plan to use To have this knowledge you must either obtain the information yourself by carefully testing first high dilutions and then gradually increased concentrations on a number of normal skins (3–10 persons usually suffice) or you must rely on the experience of others garnered for a large variety of substances and vehicles used in many thousands of tests each Follow Table 21 which gives the standard concentrations and vehicles for patch testing always making sure that your substances are of known purity that your *concentrations and vehicles* are exactly as specified and that your tests are applied and carried out in a meticulous and orthodox fashion

11 Don t allow a test which is causing great discomfort from burning or severe itching to remain in place instruct patients to remove such tests

IMMUNOLOGIC TREATMENT

The management of eczematous contact type allergic dermatitis usually depends mainly on correct *local, external therapy* supple mented by a few rational general measures and of course by the avoidance of eliciting allergens *With the exception of this avoidance of allergens no available immunologic method is of general value* In acute cases including those of plant dermatitis immunologic treatment is generally unnecessary Furthermore the administration of most of the extracts available at present seems to favor exacerba tions and to be *contraindicated* (p 84) However in some cases of *chronic* allergic contact type dermatitis due to plants or plant prod ucts (ragweed timothy chrysanthemum etc) hyposensitization with specific extracts (lipoid or oil fractions) may be of benefit perhaps reducing reactions to the chronic recurrent exposures The specific measures for treating chronic eczematous dermatitis from plants and allied agents are therefore the only ones to be detailed here

HYPOSENSITIZING PROCEDURES FOR TREATMENT OF CHRONIC PLANT DERMATITIS —*Indications* —Specific hyposensitization may be of value in severe cases of long standing chronic or chronically recurrent dermatitis in which hypersensitivity to the oily fraction of the particular plant or similar agent has *been proved* (patch test) and in which *avoidance of the allergen is impossible*

Materials —For specific treatment by oral administration oil ex tracts of poison ivy and a few other plants and allergenic agents can be purchased from firms listed on pages 301 f Other extracts must be specially prepared at the physician s request.

Methods —Intramuscular Injection The extract is given by deep intramuscular injection in the manner specified on page 82 using precautions to avoid contact of the allergen with the skin It is wise to start with small doses and to increase gradually provided there are no signs of intolerance The size of the initial dose and the rate of increase should be guided by the level of sensitivity deter

mined by clinical data and the results of preceding patch tests That concentration which just suffices to produce a slight erythema under a patch test is considered about optimal for the first injection. Injections of 0.2–1 cc. are given once weekly for six weeks or until the desired improvement has been obtained and maintained. Sometimes injections at intervals of two weeks to two months suffice to maintain the beneficial effect once it has been achieved.

Oral Administration. Treatment by oral administration of the specific oil extract is carried out in a manner similar to that specified on page 302 for prophylaxis

Contraindications and Dangers—*Acute* eczematous plant dermatitis is ordinarily self limited and yields readily to correct topical therapy There is therefore *little or no need* for specific therapy and any improvement which might be obtained by specific injections is generally outweighed by the considerable risk of causing exacerbation spread and prolongation of the dermatitis Until there is further evidence of the regularity of benefits from therapeutic injections of allergenic extracts we cannot recommend their general use in the treatment of plant dermatitis in the acute stages

On the other hand in *chronic* and *protracted* cases in which there is continued unavoidable exposure to the plant allergens or related substances the physician may decide that an attempt at specific treatment is warranted. The contraindications and dangers of the therapeutic injections are those cited for prophylactic injections (p 305) When flare ups or aggravations of the dermatitis occur or when other local or general signs of intolerance are elicited the injections of allergen should be interrupted at once If the conditions in the particular case make further specific treatment seem highly desirable the attempts may be resumed cautiously and *after* all manifestations of intolerance have abated At the resumption of treatment the initial injection should be no greater than 1/100 or even 1/1 000 of the dose which produced reactions of intolerance and the dose should be increased gradually and cautiously

IMMUNITY

Relative Immunity Acquired through Natural Exposures—All evidence indicates that acquired specific immunity or hypo or de sensitization is

1 Not of regular occurrence
2 Not absolute but only relative or quantitative in degree,
3 Not permanent but transitory

Nevertheless there is no doubt that some persons repeatedly and chronically exposed to eczematogenic allergens acquire a significant degree of tolerance Thus some (by no means all) persons who at first suffer from eczematous allergic dermatitis from certain contact type allergens will if they continue to submit to the exposures develop significant degrees of clinical resistance (hardening) They will no longer react with dermatitis when exposed to the original dermatitis producing concentrations of the allergen

However the often *rela i e* nature of this acquired resistance is seen in the fact that many of the hardened persons again develop dermatitis if the exposures to the allergen are increased in quantity or otherwise intensified And in most patients having great original sensitivity or massive exposures to po en allergens the evidence of hyposensitization or hardening is virtually absent

The often *transitory* nature of any acquired resistance is demonstrated by the fact that many hardened individuals maintain their resistan e to the effects of the allergen just so long as chronic repeated exposures are continued without major interruption But let the exposures be interrupted for even a few days or weeks (unemployment sickness vacation change of work etc) and the first re exposure again produces the dermatitis in some of the 'hardened individuals Then with continued uninterrupted exposures this new state of sensitivity may either persist or may again be replaced by acclimatization or "hardening"

Relative Immunity Produced by Deliberate Specific Hyposensiti ation—Here again the evidence indicates that any hyposensitization or immunity which can be produced must be both *relative* and *transitory* The relative or quantitative nature of the acquired resistance is apparent for individuals hyposensitized by injections of

specific plant extracts will often be resistant to dermatitis from cer tain clinical exposures to the plant but will react when the exposures are increased in quantity or otherwise intensified.

Thus persons who have received a series of specific hyposensitizing injections with plant oils may for some time be free from attack on ordinary clinical exposures but usually react to a chance extraordinarily intense clinical exposure or react when the plant is deliberately and vigorously applied or when patch tests are performed with potent plant extracts.

The transitory nature of the effect is evident for even when most successful the specific measures usually confer clinical resistance to dermatitis for only one season or at best and in exceptional cases for two or three seasons To maintain clinical resistance the specific measures must be administered repeatedly and at a relatively short time before each of the expected exposures

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

The high and costly incidence of eczematous contact type allergic dermatitis in workers and in the public at large could probably be significantly reduced by the correct and general prophylactic use of patch tests

Patch test procedures may be used for this purpose in

A *Bioassay of Materials to Select Those Less Likely to Sensitize* (p 18)—The comparative *sensitizing index* or *sensitizing poten tial* of two or more materials is ascertained by the following tests

1 Patch tests with the materials being assayed and compared are performed on a large series of subjects and whenever possible the materials eliciting the smallest number of reactions are selected

2 The materials being assayed and compared are applied to a series of test individuals in potentially sensitizing concentrations and whenever possible the materials producing the smallest num ber of sensitizations are selected

B *Selection of Individuals Less Likely to Develop Allergic Ec zematous Dermatitis* (p 22)—There are two methods of value

1 Routine patch tests with a series of common eczematogenic allergens are performed on each individual of the group This permits prophylaxis by selecting those persons giving the least reactions and therefore on the whole less likely to become sensitized by exposures to new eczematogenic allergens

2 Patch tests with the *particular* allergenic agents to which the candidate will be exposed. This permits prophylaxis by eliminating those persons who are unsuitable because of pre-existing hypersensitivity to the particular allergens in question

Obviously *these methods should not be relied on alone but should be used in conjunction with all other available methods for the prevention of contact type eczematous dermatitis* It is equally obvious that the patch test methods will help to prevent or to control only the truly allergic eczematous contact type eruptions and their sequelae and not other eczemas or other dermatoses

The industrial and general public incapacitation produced by the allergic eczematous eruptions is so high that these diseases constitute a major industrial and public health problem In addition allergic eczematous eruptions lead to many other incapacitating affections *(a)* by forming portals of entry and contributing suitable soil for streptococci, staphylococci erysipelothrix tubercle bacilli treponemas viruses fungi and other micro-organisms and *(b)* by trigger action in determining the inception exacerbation or localization of other skin disturbances such as for example psoriasis and lichen planus (isomorphic reaction)

Fungous Infections, Trichophytosis

Ringworm dermatophytosis epidermophytosis tinea corporis tinea pedis tinea cruris tinea capitis tinea barbae athlete s foot jock itch and barber s itch are among the terms commonly used to describe manifestations of fungous infections

First infection with many of the pathogenic dermatophytes (fungi producing more or less superficial infections of the skin hair and/or nails) is generally followed by an *incubation period* usually extend

ing from five days to three weeks Thereupon the disease becomes clinically manifest and the altered skin reactivity is demonstrable by specific sensitivity to fungous extracts (trichophytins oidiomycins etc) injected intracutaneously

Since many adults in modern communities have at some time had a skin infection with the common pathogenic fungi (e g athletes foot jock itch intertrigo) and since the resulting skin sensitization may be long lasting or permanent a *positive reaction to a trichophytin test is of little or no diagnostic significance* Thus the immunologic situation and the diagnostic value of the skin test with fungous extracts are analogous to those with tuberculin i e., positive reactions to trichophytin or oidiomycin indicate only that a previous sensitizing infection has taken place The skin reactions in adults do not usually throw light on the cause of a presenting lesion

Whereas infections with monilias (oidiomycetes) produce a skin sensitization to oidiomycin and not to trichophytin achorions epidermophytons trichophytons and microsporons apparently all have some strongly allergenic common denominators present in the extracts known as trichophytins For this reason trichophytins can be used in testing for sensitivity produced by achorions epidermophytons trichophytons or microsporons Trichophytin *cannot be used* for evidence of exposure to monilias blastomycetes sporotrichons coccidioides and fungi other than those mentioned here

(It is probable that trichophytons and perhaps other pathogenic fungi have antigens in common with those contained in penicillin This may account for the vesicular and other reactions resembling fungous diseases which are so commonly seen on hands groins etc following penicillin administrations)

INCUBATION PERIOD

Generally not ascertainable in superficial infections of the non hairy skin Five to 14–21 days in infections of hairy areas

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

SKIN TEST WITH TRICHOPHYTIN —*Indications*—This is generally of very limited differential diagnostic value but is sometimes of value in special problems of differential diagnosis (see Table 22)

Material—Trichophytin is prepared from cultures of trichophytons and/or immunologically related fungi such as epidermophytons and microsporons It is commercially available from

Lederle Laboratories Inc Trichophytin 1 30 in 0 5 cc. and 5 cc vials

Eli Lilly and Co Trichophyton UFA (undenatured fungus antigen) standardized to 5 mg total nitrogen per 100 cc, in 5 cc vials. Dilute 1 5 for skin test

Ernst Bischoff Co Inc Dermotricofitin in 2 5 cc. vials (This extract is said to contain oidium like fungi in addition to trichophyton and immunologically related fungi)

Lederle Laboratories Inc Dermatomycins a standard mixture of trichophytin and oidiomycin

Methods—1 Late Tuberculin Type Response to Trichophytin This is the late (24–48 hour) papular and inflammatory tuberculin type reaction Intracutaneous injection of 0 1 cc of trichophytin is given usually in the flexor aspect of the forearm or arm and 0 1 cc of control extract (e g oidiomycin or blank medium) is injected into a symmetrically placed area on the other arm The test is read at 24–48–72 hours

Description and Evaluation of Reaction—Inflammatory erythema and infiltration appear at 24–48 hours and usually persist for two to four or more days and may persist up to several weeks Persistent reaction may become eczematous lichenified and scaly The degree of sensitivity is indicated by the area and the severity of erythema *induration and edema* (about 1–3 *cm in diameter*) The reaction should be considered positive only if the reaction at the trichophytin site is significantly greater than the reaction at the control site

A *positive* reaction indicates that the individual has at some time previously had a sensitizing infection with trichophytons or immuno-

logically related fungi. It does *not* necessarily signify that the presenting signs of the disease being investigated are caused by fungous infection. (Once established the skin sensitivity to trichophytin may last for months, years or life.)

TABLE 22.—SPECIAL INSTANCES IN WHICH TRICHOPHYTIN TEST MAY BE OF VALUE IN DIFFERENTIAL DIAGNOSIS

Trichophytin Test for 24–72 Hour Late Inflammatory Reactions

More inclined to be positive	*Less inclined to be positive*
Secondary eczematous vesicular eruptions of hands and other areas (dermatophytids, epidermophytids)	Eczematous contact type dermatitis, nummular eczema, pompholyx, other nonfungous eruptions of the glabrous skin
Deeper fungous infections of hairy regions (scalp, beard, etc.) caused by zoophilic fungi (Trichophyton gypseum, Microsporon lanosum) (See Table 23)	Fungous infections of hairy regions (scalp, beard, etc.) caused by anthropophilic fungi (e.g. Microsporon audouini) (See Table 23)
Secondary eruptions associated with deeper fungous infections of hairy areas (trichophytids, microsporids, favids)	Diseases of the hair and hairy areas not due to fungi

A *negative* reaction indicates (1) that the individual has never had a sensitizing infection with trichophyton or immunologically related fungi, (2) that the individual has been exposed to fungi but is still in the incubation period of infection, or (3) that the individual has been exposed to trichophytons or immunologically related fungi but is in a state of anergy (negative nonspecific lack of reaction or positive specific and acquired resistance; see section on tuberculoderms).

Table 23 presents the important data on fungous infections of the scalp and other hairy areas and shows the significance of immunologic influences and the value of the trichophytin test in differential diagnosis.

Contraindications and Dangers.—Not infrequently, particularly in acute deep primary lesions and in acute secondary eruptions (trichophytids, epidermophytids, dermatophytids or, vulgarly, "ids")

TABLE 23.—CONTRASTING ZOOPHILIC AND ANTHROPOPHILIC FUNGI

Classification of Fungi	A. Characteristics of Diseases Produced in Man	B. Characteristics of Diseases Produced in Lower Animals
I. ZOOPHILIC (animal) pathogenic fungi commonly affecting lower animals and occasionally man (e.g., *Trichophyton gypseum, Microsporum lanosum*)	1. Lesions tend to be deep (in hairy areas), marked *inflammatory response, even to* destruction of tissues	1. Lesions superficial, with little inflammation
	2. Not highly infectious from man to man; rarely endemic or epidemic	2. Highly infectious from animal to animal (epidemic and endemic)
	3. Micro-organisms are relatively scarce in the lesions and often difficult to demonstrate by direct examination, *especially* in later stages	3. Micro-organisms numerous and can be demonstrated with relative ease by direct *examination*
	4. Histological examinations show tendency to development of tuberculoid structures, especially in later stages	4. No tendency to formation of tuberculoid structures
	5. Reaction to trichophytin skin test usually strong, not only local but often also focal and systemic reactions	5. Reaction to trichophytin skin test usually weak *or absent*
	6. Relatively strong tendency to spontaneous healing; hence relatively favorable response to both local and immunologic therapy (trichophytin injection)	6. Little or no tendency to spontaneous healing; relatively resistant to local and immunologic therapy

From Sulzberger, M. B.: *Dermatologic Allergy* (Springfield, Ill.: Charles C Thomas, Publisher, 1940).

TABLE 23 CONTINUED—CONTRASTING ZOOPHILIC AND ANTHROPOPHILIC FUNGI

Cl f F gi	A Ch p d d M f D	B Ch p d d l w A m l f D
II ANTHROPOPHILIC (h ma) path ge s l e f gi com mo ly affect g m a d ot lowe im ls (e g. *Micr sporo and sum*)	1 Lesio s t d to be s pe fic l wi h m m l s flamma o (sphl gm t c)	1 Ofte p h g n c for n m l (e g. M cro po a d l M crospo on mi im m etc.) wh n l s o re prod ced by cert fu gi such as ep de m phyto s they re often deep and i flamm tory a d
	2 Highly fect o s from m n to ma ft n epid mic a d d mic	2 Not highly infectious from im l to an mal
	3 M ro-o g sm cl ively mero s ea ly demo tra ed by d ect e ami on all stages	3
	4 No te de cy to t berculo d structures	4
	5 T chophytin kin tests as a rule n g t e prod ce only weak react ons	5 I uffic ently studied beca se s cces f l inoculations of l boratory a mals w th import nt h ma path gens are too f w in succe sf l l tances there seems to be a t dency toward characteri cs l ted nder A1 of the zooph lic f ngi
	6 Littl or no te de cy to spo taneo s heal g (except t p berty in M cro poro do m) local a d mmu logic h rapy ge erally i ffecti roe tg n y p la comm ly i d cated i calp ca es	6

local flare ups exacerbations and dissemination occur after exposure to trichophytin The reactions may be severe and may cause long lasting widespread dermatoses including exfoliating erythrodermas In superficial infections there is rarely fever or malaise In deep fungous infections of hairy areas there are often local flare ups, lymph node enlargements and systemic reactions such as fever malaise and headaches

2 Immediate Urticarial Response to Trichophytin In addition to the late tuberculin type response there is an immediate urticarial response to trichophytin This is much less common than the tuberculin type response and its full significance is not well understood The urticarial reaction is read and evaluated as usual 15–20 minutes after the intracutaneous injection of *0 01–0 02* cc of trichophytin (p 39) The response should be considered positive only if it is significantly greater than that to the simultaneous injection of equivalent amounts of a control extract (e g oidiomycin blank medium etc) in a symmetrically situated site

Some but not all of the patients showing immediate urticarial responses to trichophytin have circulating passive transfer antibodies of Prausnitz Kustner type

The early response may be of occasional diagnostic value owing to the fact that most of the early responses have been found in *(a)* chronic Trichophyton purpureum infections, *(b)* recurrent erysipelas like swellings cellulitis lymphangitis (usually of legs) presumably due to fungi *(c)* asthma, rhinitis urticarias presumably due to products of skin pathogenic fungi

TREATMENT

SPECIFIC HYPOSENSITIZATION —Hyposensitization with trichophytin is *generally of little or no value* in the treatment of superficial fungous infections and ids However in certain exceptional selected and proved cases of dermatophytids which have been resistant to all other established forms of treatment hyposensitization has shown itself of value The same holds true in selected cases of erysipelas like dermatophytids

Materials

Lederle Laboratories Inc. Trichophytin, 1 30 in 5 [illegible] *Technic* hyposensitization can usually be carried out [illegible] 1 30 extract at the start, injections are given at four [illegible] day intervals giving one 0 05 cc. and five 0 1 cc [illegible] cutaneously then intracutaneous injections of 0 1 [illegible] one or more sites increasing the total dose as [illegible] continued at one two or three week intervals for [illegible] months

In unusually sensitive patients higher than 1 30 [illegible] of trichophytin can be used (e g., 1 1 000–1 100) [illegible] Lederle 1 30 trichophytin can be diluted 3–30 times with [illegible] ile physiologic saline solution. The following two [illegible] may be used

Eli Lilly and Co Trichophyton 'UFA (undenatured [illegible] antigen) in 5 cc. vials. *Technic* hyposensitization [illegible] are given intracutaneously three times weekly or [illegible] once weekly starting with a 1 100 000 dilution [illegible] 0 2 cc. and 0 3 cc doses then doses of 0 05 [illegible] 0 2 cc. and 0 3 cc. of 1 10 000 dilution followed by [illegible] size doses of successive dilutions of 1 1 000 1 100, [illegible] indicated. As soon as improvement is observed, the [illegible] maintained at that level.

Ernst Bischoff Co., Inc. Dermatomycol in boxes [illegible] ampules in graduated strengths for initial course [illegible] of 10 cc with self sealing stoppers for both [illegible] quent course This extract is reported to contain [illegible] monilias and oidium like fungi in addition to [illegible] and immunologically related fungi *Technic* [illegible] is started with a course of five intramuscular [illegible] 0 1 0 3 0 5 0 7 and 1 cc at intervals of [illegible] then 2 cc intramuscularly at intervals of [illegible] for as long as indicated If improvement [illegible] takes place favorable results may be obtained by giving a few alternate treatments of 0 1 cc. of dermatomycol [illegible] neously and the usual maintenance dose of dermatomycol intramuscularly

Contraindications and Dangers.—With proper precautions hyposensitization with trichophytin is generally a safe therapeutic procedure Dosage has to be adjusted according to the patient s local and general response to injections If a large local reaction or a focal or systemic reaction occurs after injection the next dose should *not be more than 1 100 as great as the dose which caused the reaction*

PASSIVE IMMUNIZATION.—None available

IMMUNITY

Natural immunity is regularly acquired in tinea capitis due to Microsporon audouini infection This even without treatment *practically always clears up at or about the age of puberty* Microsporon lanosum and other zoophilic microsporon infections of the scalp also tend to spontaneous healing particularly at puberty

Some degree of purely *local immunity* is probably *acquired* by most individuals infected with trichophytons or immunologically related fungi Thus there is usually a zone of immunity or at least of relative increase in resistance surrounding active growing fungous lesions This local immunity limits peripheral extension of the infection In general the more marked the inflammatory reaction caused by the particular fungus the greater the local immunity

Some increase in general resistance is seen after some infections particularly those caused by species of fungi which tend to cause marked inflammatory reactions and strongly positive late trichophytin responses But there is *no regular increase in resistance* that could lead to permanent protection against recurrences of fungous disease of the glabrous skin On the contrary there is an apparent tendency to increased susceptibility and to recurrences in many patients with such fungous infections as athlete s foot and tinea cruris As stated repeated injections with increasing doses of trichophytin will often bring about a significant (but probably usually temporary) decrease of the skin sensitivity to fungous allergens (trichophytin)

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

In this country particularly in city populations schools military establishments etc there is a high incidence of present and past in

ections with trichophytons or immunologically related fungi However immunologic procedures are generally of *no practical importance in the control* of the dissemination or activation of diseases caused by these fungi. General skin hygiene proper clothing properly fitted and perforated shoes or sandals etc local prophylaxis with correct drying of feet conscientious use of foot powders etc are the only known preventive measures

Herpes Simplex ("Fever Blisters," "Cold Sores," Sun Blisters)

INCUBATION PERIOD

Generally not ascertainable

PROPHYLAXIS

1 SMALLPOX VACCINATION —*Indications* —A nonspecific (or crossed?) immunization through smallpox vaccination is apparently of prophylactic value in interrupting repeated recurrences in *some* cases of *recurrent* herpes simplex

Materials and Method —Materials are listed in the section on smallpox Six to 20 vaccinations by the usual multiple puncture method are given at weekly intervals irrespective of whether or not there is a take

Contraindications and Dangers —There is danger of vaccinia (p 160) in the presence of open or scratched skin lesions elsewhere (e g in eczemas atopic dermatitis etc) There is also some risk of severe reaction on first vaccination in persons who have never previously been vaccinated or who have lost their immunity

2 BLISTER FLUID VACCINATION —The blister contents are removed and inoculation is performed by the scratch method or by intracutaneous injection The available experience is not sufficient to prove this method of general value

3 INJECTIONS OF KILLED HERPES VIRUS —The material is made from suspensions of herpes virus from inoculated chick embryos or laboratory animals (e g heat formalin or phenol killed

virus in mouse brain— herpene) The available experience is not sufficient to prove the use of any type of killed virus suspension to be of general value

DIAGNOSIS

Intracutaneous skin tests are performed with *herpene* a heat killed mouse brain virus which is not commercially available There is not sufficient experience to prove this test of general value

IMMUNITY

Since the virus of herpes simplex is almost always present on most skins and mucous membranes natural or acquired immunity is probably almost continuous in most persons However clinical resistance or immunity varies greatly from individual to individual site to site and time to time[1] Given sufficient provocation the dormant virus will produce lesions in almost all persons Thus up to 90 per cent of normal persons will have an attack if their temperature is rapidly elevated above 105 F and maintained there for a few hours

In *susceptible individuals* the local immunity can be broken or reduced by different agents which act as trigger factors or synergists (fever specific foods—chocolate nuts caviar shellfish etc drugs —iodides bromides etc physical agents—light wind endocrine changes—menses pregnancy intercourse [?] psychic influences [?] etc)

In some cases permanent or temporary clinical immunity may follow the measures described under prophylaxis An attack may be followed by local immunity which is generally of short duration However in many persons attacks appear to favor an increased susceptibility rather than an increased resistance

Leprosy

INCUBATION PERIOD

Probably months to many years Cases have been reported with presumptive incubation periods of 40 and more years

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

Diagnosis by skin tests with different types of extracts of infected organs (lepromin leprolin leprin etc) is generally of little or no diagnostic value for the significance of positive and negative re actions to such tests is not clearly understood Certain forms of leprosy (tuberculoid and neural types) are said to give a higher in cidence of delayed positive reactions (three or more weeks after in jection) than other forms (lepromatous types)

Materials are prepared from infected human tissues and are not generally available in the United States

TREATMENT

No immunologic method available

IMMUNITY

Infected persons and those with burned-out cases appear to be immune to clinical manifestations following new infections More over many persons seem to have a constitutional clinical im munity and escape the clinical disease despite long and intensive exposures

There is obviously great individual variation in susceptibility The incidence of immunity appears to be significantly higher in adults and old persons than in infants and young children Apparent ly in addition to the constitution and age of an individual *regional environmental* and *climatic conditions* play determining roles that contribute to immunity or susceptibility Thus leprosy can be transmitted only in certain geographic areas and appears to be for all practical purposes a nontransmissible disease in all other regions of the globe

The evidences of local immunity at the site of cutaneous lesions are similar to those described for syphilis

EPIDEMIOLOGY AND PUBLIC HEALTH

In those regions of the earth in which leprosy is transmissible the prevention of dissemination depends on general hygiene sanita tion and the segregation of lepers

It may be that no public health measures are necessary in localities in which leprosy is not transmissible (e g in the United States—in New York and in most other states except those on the gulf coast in most of Europe except the Scandinavian countries and one region in the Canton of Wallis in Switzerland etc etc)

For reasons of convenience leprosaria are usually located in places where leprosy is transmissible and endemic This may well be an unfortunate choice of localities for it might be a better public health and therapeutic measure to place leprosaria so as to profit by the local geographic and environmental factors which confer immunity

Lymphogranuloma Venereum

This disease is also known as lymphopathia venerea lymphogranuloma inguinale tropical bubo climatic bubo anorectal syndrome (syphilome anorectale) ulcus vulvae elephantiasticum and esthiomene

INCUBATION PERIOD

Probably days to weeks

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

Skin Test—Tests with lymphogranuloma antigen with antigen from human pus (Frei test) and with antigens of other origins are generally valuable in the diagnosis of lymphogranuloma venereum

Indications—Skin tests are generally useful in

a) All buboes in enlarged and/or breaking down and draining inguinal nodes and in similar conditions of unknown etiology in lymph nodes of other body regions

b) Genital lesions particularly in herpetiform lesions of unknown etiology

c) Chronic edema and lymphedema with or without ulceration of genital and perigenital structures of male and female

d) Rectal strictures proctitis and rectal discharges of unknown etiology

e) Nonspecific urethritis (some authors hold that this condition may in some cases be a manifestation of lymphogranuloma venereum)

Materials—1 Frei antigen is prepared from pus obtained by sterile aspiration of unopened fluctuant human lymph nodes in proved cases of lymphogranuloma venereum (i e typical, uncomplicated early cases with positive Frei test) 2 Lymphogranuloma antigen is prepared from the chorioallantoic membrane of chick embryos which have been infected with lymphogranuloma venereum.

E. R. Squibb & Sons Lygranum S T (lymphogranuloma venereum antigen of chick embryo origin for skin test) and Lygranum S T Control (normal chick embryo antigen for skin test control) are packaged together in single test packages and 10 test packages

Lederle Laboratories Inc. Frei Antigen (chick embryo origin) and Frei Antigen Control (chick embryo origin) are packaged together in 0 1 cc. syringes (single test) and in rubber stoppered 1 cc. vials (10 tests)

Method—Intracutaneous injection of 0 1 cc of the antigen is given usually in the flexor aspect of the forearm or arm When antigens of nonhuman origin are used 0 1 cc of the control material is injected intracutaneously in a symmetrically placed area on the opposite arm

Time and Method of Reading Test—Read at 48–72–96 hours According to some investigators the papule should measure 7 mm or more in diameter It is further stated that to consider a response positive when antigen of nonhuman origin is used the diameter of the reaction at the test site should be at least 7 mm greater than the diameter of the reaction at the control site

Description and Evaluation of Reaction—A positive reaction consists of a 48 hour type erythematous papular or infiltrated reaction which usually persists at least several days to a week The center of the papule is pustular at times herpetiform and other

types of reaction are occasionally encountered. According to some investigators a reaction which is less than 7 mm in diameter o a reaction at the test site which is about the same size as that at the control site should be considered negative In case of a question able result it is advisable to repeat the test with a *different* type of antigen preferably one of human origin (Frei test)

Significance of Positive and Negative Results—A *positive* reaction signifies present or past infection with lymphogranuloma venereum virus or a related virus but does not necessarily signify that the presenting disease is due to lymphogranuloma venereum infection Once established the skin sensitivity lasts for years and perhaps for life The capacity of the skin to react is sometimes established within five to seven days after infection but it may take weeks or even months to develop

A *negative* reaction signifies (1) that the patient has not been infected with lymphogranuloma venereum (2) that infection has taken place so recently that the skin has not yet become sensitive in which case repetition of the test is of course indicated[7] or (3) that the individual is in a state of anergy In exceptional cases and under certain conditions (cachexia acute exanthems early syphilis etc) the reaction to the lymphogranuloma venereum skin test may be negative despite present or past infection

Contraindications and Dangers—Generally none sometimes headache fever malaise erythema nodosum like eruption and other transitory manifestations of no serious consequence may develop Use of chick embryo antigen in atopic persons highly sensitive to egg is contraindicated.

TREATMENT

Immunologic procedures are at present of limited or questionable value particularly in relation to the probable value of sulfonamide

[7]It has often been shown that repeated injections of Frei vaccine do not of themselves specifically sensitize the skin. For experimental purposes one of the authors gave himself 15 successive intracutaneous injections of Frei antigen without causing the slightest skin sensitization.

and other therapy However in persons who do not tolerate sulfonamides intravenous injections of human lymphogranuloma venereum antigen or of chick embryo antigen can be tried Dosage is 0 3 cc of the antigen three times weekly for six weeks to many months

IMMUNITY

A "chancre immunity probably exists and possibly also both natural and acquired general immunity of long duration (It has recently been reported that *reinfection* occurred in some patients who had been under intensive treatment with sulfonamides)

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

In some sections of the population and in some localities in the United States especially in the Negro population and usually in groups with considerable sexual promiscuity there is a relatively high incidence of positive reactions to lymphogranuloma venereum skin tests *Many of these skin reactions occur in individuals who do not present and presumably never have presented clearcut clinical manifestations of lymphogranuloma venereum* These reactions should not necessarily be considered false positives for a high degree of specificity of the Frei test has been established Subclinical infections with lymphogranuloma venereum virus are probably not infrequent and there may be many carriers particularly among women It is also possible that some of the positive reactions are cross reactions attributable to infection not with the virus of lymphogranuloma venereum but with other viruses (psittacosis infectious choreomeningitis?)

Malleus (Glanders)

INCUBATION PERIOD

Three to five days

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

The differential diagnostic value of skin tests with *mallein* has not been established For methods of intracutaneous injection reading and evaluation of results see skin tests with tuberculin trichophytin etc

Materials—Mallein is an extract prepared from cultures of Malleomyces mallei It is not commercially available

TREATMENT

The value of immunologic therapy with specific antimalleus serum is not established Materials are generally not available for human use

Monilia Infections

Monilia infections include moniliasis moniliids oidiomycosis oidiomycids interdigital erosion water bed mycosis and monilial onychomycosis Monilias must be considered at best facultative pathogens Infections of the skin gastrointestinal tract and other sites occur early in life in a great many—perhaps in almost all—persons Skin disease caused by monilias is therefore dependent on the coexistence of constitutional and/or local factors which diminish resistance (moisture heat maceration contact dermatitis seborrheic dermatitis diabetes etc)

As in tuberculin and trichophytin tests *a positive reaction* to the intracutaneous injection of oidiomycin *signifies only a previous sensitizing exposure*

INCUBATION PERIOD

Generally not ascertainable

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

The skin test with *oidiomycin* is of little or no diagnostic value It is generally *of value as a control injection for use with the tri*chophytin test

Materials—Oidiomycin is prepared from cultures of Monilia albicans.
Lederle Laboratories, Inc. Oidiomycin 1 100 in 0 5 cc. vials and 5 cc. vials

(As a rule, manufacturers prepare trichophytin and oidiomycin by a similar technic and on the same kind of medium. Thus it is possible to use oidiomycin of a given manufacture as a control for the trichophytin of the same manufacture When both oidiomycin and trichophytin elicit equally strong positive reactions the "blank medium" must be used as control.)

Methods—1 For late 24–48 hour reaction an intracutaneous injection of 0 1 cc of oidiomycin is given in the flexor aspect of the forearm or arm and 0 1 cc of the control extract (e g. trichophytin) is injected in a corresponding area on the other arm

2 For early (urticarial) reaction an intracutaneous injection of 0 01–0 02 cc oidiomycin is given in the flexor aspect of the forearm or arm and 0 01–0 02 cc of the control extract (e g trichophytin) is injected in a corresponding area on the other arm

The *time and method of reading the tests* and the description and evaluation of reactions are given under trichophytin tests (p 340)

Contraindications and Dangers—Generally there are none but in cases of generalized eruptions flare ups dissemination and aggravation of the dermatosis may occur

TREATMENT

Immunologic methods have not been proved of therapeutic value The injection of specific extracts follows the schedule recommended for trichophytins

IMMUNITY

It has not been proved that immunologic changes lead to an increase in local or systemic resistance that could result in protection against monilial skin disease

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Immunologic procedures are of no practical importance in the control of diseases caused by monilias

"Physical Allergies" of the Skin

Many persons are *hypersensitive* to so called physical agents such as stroking and other trauma, light cold and heat These individuals react in various ways to exposures which quantitatively are significantly below those required to produce any untoward reaction in normal persons The pathologic changes elicited by physical agents are varied and are by no means always based on specifically acquired allergic hypersensitivities or on particular immunologic mechanisms

Actually nonimmunologic mechanisms are the bases of many of the hypersensitivities to physical influences This can be clearly seen in certain obviously nonimmunologic cutaneous reactions to physical agents Examples are the hypersensitivity to stroking and other trauma seen in persons with vasomotor instability (tache cerebrale vasomotor dermographism) the excessive skin damage bullae or detachment of the epidermis produced by trauma in pemphigus or in epidermolysis bullosa or the excessive reactions to light (as seen in fair skinned freckled and red haired persons in albinos in hydroa vacciniforme in xeroderma pigmentosum in pellagra in lupus erythematosus in Kiehl s melanosis in persons exposed to certain tars oils perfumes, extracts of fruits or vegetables dyes certain ingested foods [favism fagopyrism] or certain drugs etc)

But in addition to these clearly *nonimmunologic* hypersensitivities there are some *urticarial responses to friction or to pressure to light or to cold or to heat* which appear to be *based on true immunologic sensitization to some antigen which the respective physical agents produce or release in the tissues of the skin*

It seems to us that the simplest tenable hypothesis is that the tissues contain an antigen precursor or "proantigen which becomes an active or "free" antigen under the effects of the physical agent. There is unequivocal idence that in certain cases of light urticaria cold urticaria, and perhap also in exceptional forms of dermographism, these hypersensitivities *n be transferred to normal skins with constituents of the patient's rum which appear to correspond rather closely to the*

Prausnitz Kustner antibodies Only these cases are here considered to be proved instances of physical allergy

In all these urticarial sensitivities to physical agents the *period of refractoriness to sensitization* is apparently as variable as in other allergies In none has the *incubation period of sensitization* been ascertainable

The *reaction time* is a matter of seconds to a few minutes just as in other urticarial responses

PROPHYLAXIS AND TREATMENT

PHYSICAL ALLERGIES IN GENERAL —Prophylaxis and treatment consist essentially in *preventing or reducing exposures* to the physical agents eliciting the reaction in the particular case In addition the nonspecific prophylactic and therapeutic measures recommended in urticaria (p 388) and/or in atopic dermatoses (p 268) have been reported to be of value in some cases

Elimination of foci of infection may be one measure worthy of serious consideration Liver and gallbladder diseases have often been considered causative in these conditions especially in cases of hypersensitivity to light

Pyribenzamine (Ciba) and Benadryl (Parke Davis) in doses of 150–400 mg daily are of pronounced benefit in many but by no means all cases of physical allergy

ALLERGIC URTICARIA FACTITIA OR DERMOGRAPHISM (ALLERGY TO STROKING AND OTHER TRAUMA) —In some cases of dermographism itching is severe and in others there is little or none When pruritus is distressing it can usually be reduced by having the patient take a hot bath and deliberately scrub the skin with a soft brush or a rough cloth producing large areas of whealing *while under the hot water* To avoid shock and general ill effects the procedure should be carried out carefully and gradually beginning with relatively small areas of skin and increasing daily until the entire trunk and extremities can be scrubbed In most cases it will be found that for several hours following this procedure

the itching has been abolished or greatly reduced Trauma will cause wheals just as before but the formerly associated pruritus is lessened or gone

The peculiar susceptibility that leads to dermographism can last for days weeks years or indefinitely It often disappears as sud denly and mysteriously as it appeared Transitory dermographism of a few days duration is a not uncommon accompaniment of ordinary urticaria certain drug eruptions widespread eczema and eczematous contact type dermatitis and other acute inflamed der matoses

It is most important to remember that scratch and intracutaneous skin test procedures are often sufficient to cause strong nonspecific whealing in patients with dermographism In such patients the sites of skin tests are often reacting to the trauma of scratch or injection and not to the allergen being tested Unless the physician bears this in mind many false positives will be recorded In many cases of *urticaria factitia* direct skin tests are impossible If indicated the patient s serum can be tested indirectly i e by the passive transfer or Prausnitz Kustner technic Such testing should be done by a specialist (For details of the passive transfer test see modern text books on allergy)

ALLERGIC LIGHT URTICARIA (URTICARIA SOLARIS ALLERGY TO LIGHT)—The cardinal immunologic features of this hyper sensitivity are those described for physical allergies in general In different light sensitive patients different wavelengths of the visible spectrum and/or of the ultraviolet spectrum cause the whealing Most patients in whom passive transfer antibodies were demonstrated have reacted to wavelengths below 3 700 A In per sons sensitive to wavelengths above 3 200 A exposure through ordinary window glass may produce reactions Within a few minutes after the particular wavelengths strike the skin in sufficient quantities and intensity wheals and flares appear at the exposed sites When the reaction is severe or extensive nausea headache dyspnea (asthma?) and constitutional shock reactions may appear Abortive

forms of urticaria solaris may be seen in which the skin merely becomes red or merely itches on exposure to sunlight

There is apparently no relationship between this *true urticarial allergy to light* and other forms of light hypersensitivity seen in hydroa, pellagra, lupus erythematosus etc

Prevention and Treatment—The nonspecific measures recommended for urticaria and for atopic dermatoses plus the elimination or reduction of exposures to the eliciting bands of the spectrum are indicated. Reduction of exposure can be accomplished by not going out into light or by shading with hats veils etc., or by covering all exposed areas with physical or chemical filtering agents The physical filters include clothing opaque powder filled lotions creams ointments etc Commercial chemical filters (sun protectives) include the following

1 Almay (liquid) contains tannic acid and salol

2 Dorothy Gray (creamy liquid) contains glyceryl salicylate

3 Helena Rubenstein (liquid or cream) contains menthyl anthralinate

4 Norwich (liquid) contains glyceryl para aminobenzoate

5 Skol (liquid) contains hexahydroxyethyl tannic acid, aluminium chloride salol, menthol, tertiary butyl cresol

6 Squibb (cream) contains homomenthyl salicylate

7 Sutra (liquid and cream) contains hydroquinone

Since not all persons with urticaria solaris are hypersensitive to rays in the same spectral zone the chemical filters used in a given case must absorb those wavelengths which are harmful to the particular patient If none of the commercially available preparations are helpful chemical filters of different absorbent capacities should be tried until the correct one or correct combination is found This is often a highly technical procedure requiring special knowledge and equipment

Specific Hyposensitization or Immunization—*There is no available means of specific hyposensitization or immunization in urticaria*

solaris The condition can last for days, weeks years or indefinitely [8]

There are a few reports of successful desensitization (hyposensitization) by injection of the patient's irradiated serum These however require confirmation Another method of hyposensitization which has been tried is that of repeated very short exposures to light of small well shielded areas The refractoriness to whealing which can be produced by such exposures appears to be only evanescent and local and of no practical therapeutic value The antihistaminic agents are well worthy of trial and are symptomatically beneficial in many cases

IMMUNOLOGIC COLD URTICARIA AND HEAT URTICARIA—In these the situation is similar to that described for the physical allergies to light but it is either cold or heat and not light which causes the sensitization and elicits the urticarial response (by liberating or activating the proantigen?)

Prevention and Management—These consist in the usual nonspecific measures plus *specific immunologic measures of prophylaxis and treatment* One approach is the usual avoidance or reduction of exposures to the eliciting agents In contrast to light urticaria however there is evidence that in many cases of cold urticaria as well as in some cases of heat urticaria the *repetition of gradually increasing exposures to the offending agent leads to some degree of refractoriness or hyposensitization and sometimes to considerable clinical relief*

The *specific or immunologic measures recommended in cold urticaria* are as follows

1 The patient is stroked once or twice daily with ice On each successive day a larger area of skin is stroked for example the first day one forearm the second day the whole arm the third day one arm and one forearm etc until eventually almost the entire body is being stroked twice daily

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Some investigators have held that most cases of urticaria solaris are due to photosensitizing chemicals circulating in the patient's blood and that the porphyrins liver damage and intestinal infections are important But in the truly allergic cases here considered no known directly photosensitizing nonimmunologic chemicals have been found in the blood stream.

2 The patient takes daily baths with gradually decreasing tem perature and gradually increasing periods of immersion

When the tolerance to cold has been successfully raised by these measures, the hyposensitization exposures may consist of strokings and/or baths at intervals found to be sufficient to maintain the tolerance Daily exposures may be necessary or in some cases hyposensitization can be maintained by exposures a week or more apart.

The *specific or immunologic measures of benefit in hea urticaria* may in some cases be equivalent to the hyposensitizing exposures used in cold urticaria These can be given by infra red lamps with heating pads or light cradles or hot baths or simply by swathing in blankets The principle is that of gradually increasing exposures i.e., of applying progressively higher temperatures to greater and greater body areas and for longer and longer periods Caution is necessary and a conservative beginning is advisable if shock and disagreeable by-effects are to be avoided *Maintenance* exposure may be required just as in cold urticaria

(In heat hypersensitivity muscular exercise can be used in place of outside sources of heat to supply increasing caloric exposures Thus instead of heat lamps hot baths etc gradually increased periods of exercise—if necessary while fully clothed and in a hot room—can be used in the attempts at hyposensitization)

MISCELLANEOUS REACTIONS—In addition to the relatively few proved immunologic or allergic hypersensitivities to physical agents there are numerous and varied clinical forms of skin hyper sensitivity to trauma, light, heat, cold etc As previously stated the nonimmunologic nature of many of these hypersensitivities can be proved They do not therefore come within the range of this text

There are however many other pathologic skin reactions to physical agents in which the allergic mechanism is not proved but is probable Among these are certain eczematous lichenoid papular and prurigo-like responses to light heat friction and other trauma certain erythemas and even vesiculobullous responses to physical

agents including *x rays* and *radium*, and a variety of other abnormal skin reactions to different physical forces Further discussion of such phenomena is omitted here not only because they are too little understood to be classed as proved allergic reactions but also because no immunologic methods of prevention and/or treatment are available

Sporotrichosis

INCUBATION PERIOD

Probably three days to several weeks

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

The skin test with *sporotrichin* is generally valuable in the differential diagnosis of sporotrichosis from other infections

Materials—Sporotrichin is prepared from cultures of Sporotrichum schencki It is not commercially available

Method—Intracutaneous injection of 0 1 cc of sporotrichin is given usually in the flexor aspect of the forearm or arm The test is read at 24–48–72 hours

Description and Evaluation of Reaction—The reaction appears at 24–48 hours and usually persists for several days The response is indicated by an erythematous papular or infiltrated reaction about 1–2 cm in diameter The center of the papule is pustular at times A *positive* reaction indicates that the individual has been *infected* with Sporotrichum it does not necessarily signify that the presenting signs of disease are due to sporotrichosis Once established the skin sensitivity lasts for years and probably for life In rare instances positive sporotrichin reactions may occur in patients who have been infected not with Sporotrichum but with some other related fungus which has produced a group or cross reaction

A *negative* reaction indicates that the patient has not been *infected* with Sporotrichum or that infection has taken place such a short time

before that the skin has not yet become sensitive In the latter case a later repetition of the test is of course indicated In rare instances patients with sporotrichosis are reported to have had a negative re action to the sporotrichin test (positive anergy or hypoergy?)

Contraindications and Dangers —Generally none

TREATMENT

Immunologic therapy with *sporotrichin* is said to be of value in some cases and may be tried if the patient does not respond to treat ment with potassium iodide and other therapy Injections are given as described for trichophytin or tuberculin Materials are not com mercially available

IMMUNITY

A certain degree of increase in resistance can perhaps be achieved with sporotrichin injections However there appears to be no specific acquired resistance to reinfection

Staphylodermas

Staphylodermas or pyodermas due to staphylococci, include such entities as furuncles carbuncles sweatgland abscesses (hidroadenitis suppurativa) folliculitis certain impetigos and ecthymas Staphylo coccic infections are also considered in Chapter 3

INCUBATION PERIOD

Generally not ascertainable

PROPHYLAXIS

See prophylactic treatment

DIAGNOSIS

No immunologic method available

PROPHYLACTIC TREATMENT

Prophylactic treatment with staphylococcus vaccine (allergens) combined with staphylococcus toxoid may be of considerable value in preventing recurrences in some cases of furuncles carbuncles and sweatgland abscesses Prophylactic treatment with staphylococcus

vaccine alone or with staphylococcus toxoid alone may also be tried In some cases autogenous vaccines prepared from cultures of material from the patient s own lesions are apparently superior to commercial polyvalent vaccine In others the commercial preparations are as good as or superior to the autogenous vaccine If no autogenous vaccine is available purchasable stock vaccine may be substituted and used preferably in conjunction with staphylococcus toxoid

Materials —Autogenous Vaccine is prepared from culture of staphylococci derived from the patient s own lesions it is usually filled in 10 cc vials containing 100 million and 1 000 million micro-organisms per cc

Stock Vaccine is prepared from Staphylococcus aureus and/or Staphylococcus albus and/or Staphylococcus citreus Acceptable preparations are obtainable from many reputable pharmaceutical houses. These are usually packaged in 5 cc 10 cc. 20 cc. and 30 cc. vials and contain from 250 million to 2 000 million killed micro-organisms per cc.

Staphylococcus Toxoid contains formaldehyde detoxified toxins of Staphylococcus aureus and Staphylococcus albus. Satisfactory preparations are available from a large number of reputable pharmaceutical firms The following have been accepted for inclusion in N.N.R., 1946

Lederle Laboratories, Inc. two 5 cc vials one containing 100 and one containing 1 000 necrotizing doses of toxin per cc

National Drug Co two 5 cc. vials one containing 100 and one containing 1 000 necrotizing doses of toxin per cc

Parke Davis & Co two 5 cc. vials one containing 100 and one containing 1 000 necrotizing doses of toxin per cc.

Pitman Moore Co 5 cc vials 1 000 necrotizing doses of toxin per cc

Sharp & Dohme Inc. two 5 cc. vials containing 100 and 1 000 necrotizing doses of toxin per cc. respectively

E. R. Squibb & Sons 5 cc vials 1 000 necrotizing doses of toxin per cc.

For combined treatment with Stock Vaccine and Toxoid satisfactory preparations are available from

National Drug Co Vatox in 6 cc. vials, 1 000 necrotizing doses of toxin and 2 000 million killed staphylococci per cc. *Dosage* 0 1 cc. is given intracutaneously then at four to five day intervals nine doses are given subcutaneously each dose increased by 0 1 cc. then 5–10 more subcutaneous injections of 1 cc. at weekly intervals

E R. Squibb & Sons Staphylococcus Ambotoxoid in 5 cc. vials 1 000 necrotizing doses of toxin and bacterial antigens from at least 2 000 million killed staphylococci per cc. *Dosage* at four to five day intervals 0 05 cc. and 0 1 cc. intracutaneously then subcutaneous injections are continued at seven day intervals in 0 15 cc 0 2 cc. 0 25 cc., 0 3 cc., 0 4 cc., 0 5 cc., 0 6 cc. 0 7 cc 0 8 cc 0 9 cc. and 1 cc. doses

Methods—For treatment with *autogenous* staphylococcus vaccine injections of vaccine containing 100 million micro-organisms per cc are given at four to five day intervals 0 1 cc intracutaneously and increasing doses of 0 2 0 3 0 4 0 5 0 6 0 7 0 8 and 0 9 cc subcutaneously then subcutaneous injections of vaccine containing 1 000 million micro-organisms per cc are given at seven day intervals in 0 1 0.2 0 3 0 4 0 5 0 6 0 7 0 8 0 9 and 1 cc doses

For treatment with *stock* staphylococcus vaccine injections are given at four to five day intervals 0 1 cc intracutaneously and increasing doses of 0 2 0 3 0 4 0 5, 0 6 0 7 0 8 0 9 and 1 cc subcutaneously then 10 more injections of 1 cc are given subcutaneously at weekly intervals

For treatment with staphylococcus *toxoid* injections of toxoid containing *100* skin necrotizing units per cc. are given at four to five day intervals 0 1 cc intracutaneously and increasing doses of 0.2 0 3 0 4 0 5 0 6 0 7 0 8 and 0 9 cc subcutaneously then subcutaneous injections of toxoid containing 1 000 skin necrotizing units per cc are given at seven day intervals in 0 1 0.2 0 3 0 4 0 5 0 6 0 7 0 8 0 9 and 1 cc doses

Contraindications and Dangers—Treatment with autogenous or stock staphylococcus vaccine and with staphylococcus toxoid is gen

erally a safe prophylactic procedure Dosage must be adjusted to the individual s response to injections In case of local or systemic (usu ally mild) reaction the next dose should be no more than 1/10–1/4 the dose which caused the reaction

TREATMENT

Immunologic measures are generally of very limited value How ever in furuncles carbuncles and sweatgland abscesses which are persistent and do not respond to the usual treatment measures the immunologic procedures listed under prophylaxis may be tried in therapy The use of staphylococcus antitoxin is as a rule not indi cated in the staphylodermas For its use in systemic staphylococcic infections see page 163

Immunologic prophylactic diagnostic and therapeutic procedures are generally of no value in the following staphylodermas

Ecthyma (staphylococcic)
Impetigo (Bockhart s)
Folliculitis
Sycosis barbae (barber s itch) (not a proved pyoderma)
Impetigo contagiosa (staphylococcic)
Paronychia (staphylococcic)
Infectious eczematoid dermatitis (not a proved pyoderma)
Impetiginized dermatitis (staphylococcic)

IMMUNITY

A certain degree of natural or acquired general immunity is prob ably present in most individuals An increase in resistance is some times produced by injections of staphylococcus toxoid and staphy lococcus vaccine Unfortunately furuncles carbuncles and sweat gland abscesses are often followed by a *decrease in clinical resistance* leading to recurrences or reinfections in the same in adjoining or in distant areas Local factors such as heat maceration friction scratch ing or dermatitis all may play a role in lowering local resistance Systemic and constitutional factors are apparently also of some im portance in lack of immunity (diabetes anemias seborrhea dietary deficiencies etc.)

Streptodermas

Dick toxin and Dick antitoxin have found no general use in prophylaxis diagnosis or therapy of streptodermas

Immunologic prophylactic diagnostic and therapeutic procedures are not generally useful in the following streptodermas

Erysipelas	Paronychia (streptococcic)
Ecthyma (streptococcic)	Impetiginized dermatitis (streptococcic)
Impetigo contagiosa (streptococcic)	Perlèche (streptococcic)

Specific antistreptococcus horse serum and human convalescent serum were formerly used with variable effects in erysipelas These immunologic measures have now been entirely superseded by the use of penicillin and the sulfonamides Chemotherapy and the use of antibiotics have supplanted immunotherapy in other streptodermas also

Syphilis (Lues)

INCUBATION PERIOD

Usually 10 days to 6 weeks

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

SKIN TEST —*Indications* —The skin test with luetin is generally of *no* value in primary and secondary syphilis of very *limited* value in tertiary syphilis and of *no* value in late cerebrospinal syphilis i e paresis tabes and other so-called metasyphilitic conditions

Materials —There are many different types of Luetin. The most widely used are those prepared from organs of infected individuals or from in vitro cultures of treponemes (the latter are today not considered to be quite identical with Treponema pallidum) Materials are not generally available

Method —An intracutaneous injection of 0 1 cc of luetin is given usually in the flexor aspect of the forearm or arm An intracutaneous injection of 0 1 cc of luetin control is given in a symmetrically placed area on the other arm The test is read at 24–48–72 hours

Description and Evaluation of Reaction —The reaction appears within 24–48 hours and usually persists for two to four days or more The response is indicated by an erythematous edematous and papular or indurated area usually about 1–3 cm in diameter The result should be considered positive only if the reaction at the luetin site is significantly greater than the reaction at the control site

The *reaction is not very specific or diagnostic* A *positive* reaction is sometimes elicited in late secondary and more frequently in tertiary syphilis The response is also frequently positive in persons who have received injections of agar and other nonsyphilitic allergens or to whom iodides (or bromides?) have been administered

A *negative* reaction is generally of no significance and does not rule out tertiary syphilis

Contraindications and Dangers —None

TREATMENT

No immunologic method available

IMMUNITY

Chancre immunity generally develops early sometimes *before* the appearance of the syphilitic chancre This means that shortly after the first inoculation subsequent inoculations or superinfections with the *same strain* of treponeme usually fail to produce chancres and primary complexes (cf tuberculoderms) In addition to chancre immunity in all stages of syphilis there are considerable general alterations in the tissues capacities to respond and significant local immunologic changes in and around the tissues infected by the treponeme These immunologic changes exert decisive influences on the development evolution and healing of syphilitic lesions In the skin these local immunologic influences are best recognized in ostraceous

imbricated and corymbiform lesions in the serpiginous and annular forms in kidney shaped lesions etc

In many cases *immunity to reinfection with Treponema pallidum persists even after treatment and apparent cure* Whereas the criteria for proving reinfection are difficult to establish a high incidence of reinfections has recently been reported in persons with early syphilis who have undergone intensive arsenotherapy or who have had full courses of penicillin

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Individuals with active syphilis or with long standing but burned out syphilis (latent syphilis) are immune to further clinical signs of infection.

There are no available immunologic methods for preventing infection. The eradication of syphilis would probably be a relatively rapid and certain result of the perfection of an efficient immunologic method of conferring immunity to infection

Tuberculoderms*

In the skin as in other organs the different manifestations of tuberculosis are determined largely by the size of the inoculum the virulence of the micro-organisms and the resistance of the host

One of the important factors in host resistance is the immunologic response of the tissues There is an evident obligatory association between tuberculosis and skin sensitivity to tuberculin. Individuals and populations or communities not exposed to tubercle bacilli evidence no skin sensitivity to tuberculin In these its intracutaneous injection produces no reaction

Whenever an individual encounters for the *first* time an adequate infecting inoculum of tubercle bacilli, an incubation period of from five to seven days up to three or more weeks ensues Apparently regardless of the organ or site of inoculation at the end of this incubation period the *skin* response to tuberculin has become

* See also tuberculosis Chapter 3

positive and the primary lesion and primary complex appear at the site of inoculation

In most modern civilized communities most first infections with tubercle bacilli and thus the majority of primary complexes occur either in the lungs or in the gastrointestinal tract and are clinically occult A *primary tuberculous infection of the skin with the development of a cutaneous chancre* or ulcer and with regional lymph node involvement is seen rarely except under primitive conditions of life and in communities with low hygienic standards

Both the occult infections of the viscera and the rare primary complex of the skin often take place some time during early childhood

Apparently regardless of the site of the first inoculation the skin s specific acquired alteration in its capacity to react to tuberculin remains for many years and perhaps even for life For this reason the *positive skin reaction to the tuberculin test signifies only that an adequate exposure and first infection with tubercle bacilli have taken place some time in the past* As a rule normal persons who have had such infections react to intracutaneous injection of old tuberculin Koch (OTK) in dilutions of 1 1 000 1 5 000 or 1 10 000

The tuberculin test is *specific* in that it uses an injection of the allergens of the tubercle bacillus to ascertain whether or not an infection with tubercle bacilli has taken place But it is not generally of *etiologic or diagnostic value with reference to a presenting skin condition* because the positive result is exceedingly common among all individuals except young children Therefore the positive skin reaction cannot be regarded as proof that the condition under investigation is tuberculous

Under most circumstances regardless of the site or organ of first inoculation after the first infection of the individual has taken place all subsequent inoculations of the skin with tubercle bacilli are to be classed as *secondary* i e they are reinoculations or superinoculations taking place in an individual whose tissues have already acquired a specific alteration in their capacity to react The tubercle bacilli which produce the super or reinfection of the skin may

originate from a focus in the person himself or they may come from a new outside source. They may reach the skin from without or from within, via blood stream, lymph, etc. But regardless of the origin of bacilli or of the route by which they reach the skin, the secondary lesions they produce are influenced by the immunologic changes or sensitivity which were acquired as a result of the first inoculation and which help to determine the reaction of the reinfected organism.

The various *tuberculoderms* differ radically in appearance and behavior—in course, prognosis, histologic and bacteriologic findings and epidemiologic significance. And in the different groups of tuberculoderms there is an apparent relationship between these differences in fundamental characteristics and in the particular group's characteristic immunologic response to intracutaneous injection of tuberculin. Thus, *quantitative* skin tests with *serial dilutions of tuberculin* performed in large series of individuals have shown that the level of tuberculin sensitivity tends to be somewhat different in the different types of tuberculoderms. Some types tend to a greater sensitivity than a corresponding normal group of persons (hyperergic) some to less sensitivity (hyposensitive hypoergic or relatively anergic) and some include many hyperergic as well as hypoergic cases (transitional forms)

The classification of skin tuberculosis into primary and secondary forms and the further subdivision of tuberculoderms into the three great immunologic classes (Koch Jadassohn and Lewandowsky) has established beyond question the determining influences which specific immunologic tissue sensitivity to the allergens of the tubercle bacilli exert on the form course and prognosis of all tuberculosis

We believe that a more general recognition of these immunologic facts would constitute a great advance in the understanding of the pathogenesis of all tuberculous disease

INCUBATION PERIOD

In most cases the exact incubation period is not ascertainable But in cases of *primary cutaneous infection* in which the clinical incuba

tion period has been demonstrable it has usually corresponded closely to that of experimental infections of the skin The primary lesion or chancre of the skin and the primary complex generally develop in from five days to four or more weeks after the first inoculation.

PROPHYLAXIS

No specific immunologic measures are as yet generally accepted in the United States

Neither hyposensitization by means of injection or other administration of tuberculin nor immunization through inoculation of attenuated micro-organisms e g Bacillus Calmette Guérin (BCG) is recognized in this country as a prophylactic measure of value It is well established, however that the level of skin response to tuberculin can be at least temporarily altered (reduced or increased) by such measures And, in a disease so manifestly dependent on the levels of tissue sensitivity there is hope that a practical method of immunologic prophylaxis may yet be introduced Some promising efforts in this direction include the potentiating of the tuberculin allergens through adsorbents through their incorporation in oily and fatty suspensions (aquaphor mineral oil and wetting agents etc) for deposit and slow absorption, and through the addition of synergists etc.—as well as by fractional separation and preparation of more effective antigenic mixtures

DIAGNOSIS

SKIN TESTS WITH TUBERCULIN —*Indications*—The *intracutaneous* test with tuberculin and the observation of inflammatory papular 24–48 hour type of response is generally of some value in the following diagnostic problems

1 To help exclude the existence of *any previous* tuberculous infection and thus to rule out the tuberculous nature of a presenting manifestation A negative response to undiluted or to a 1 100 or 1 1 000 dilution of OTK generally indicates that no tuberculous infection has taken place (Only in very exceptional cases is the lack of reaction due to the fact that the individual has been recently infected and is still in the incubation period required for the development of cutaneous sensitivity to tuberculin On other rare occasions

negative response may exist despite previous infection being due to a marked positive [relative] anergy as in sarcoidosis or to a negative hypoergy or anergy as in cachectic or moribund persons in spinal meningitis measles etc)

This diagnostic use of the tuberculin test is obviously of greatest practical value in *young children* The diagnostic value of the positive response to tuberculin decreases with age for in older patients a preceding (healed) tuberculous infection and a positive tuberculin reaction are to be expected in many instances regardless of the etiology of the presenting skin lesions

2 *Quantitative testing with serial dilutions* of tuberculin to ascertain the *level* of skin sensitivity This permits the classification of the patient as either more than normally skin sensitive (hypersensitive or hyperergic) as normally skin sensitive (normergic) or as less than normally skin sensitive (hyposensitive hypoergic or relatively anergic) All other things being equal on the basis of statistical probability the type of reaction favors the diagnosis of one or another group of tuberculoderms The known hyperergic transitional and hypoergic diseases are set forth in Table 25 together with their significant characteristics

It must be stressed once again that the level of cutaneous tuberculin sensitivity in any given individual indicates merely a certain statistical probability which can be weighed in evaluating the results of all other diagnostic measures

Materials—Many different extracts and suspensions of tubercle bacilli i e different forms of *tuberculin* have been developed but only three forms are in general practical use today

1 Old Tuberculin Koch (OTK) This is in the form of a sterile solution consisting of the soluble products of the tubercle bacillus (Mycobacterium tuberculosis) grown in a special liquid culture medium The finished solution should contain about 50 per cent glycerin. Satisfactory preparations are available from many reputable pharmaceutical firms and official local health agencies (p 172) These are available in packages containing (1) undiluted tuberculin, (2) undiluted tuberculin

with diluent ready for preparing desired dilutions and (3) various dilutions of tuberculin.

Undiluted tuberculin is quite stable when kept in the refrigerator The higher dilutions must be freshly prepared every one to two weeks or preferably on the day of their use

2 Purified Protein Derivative of Tuberculin (PPD) This is defined in N.N.R. 1946 as a filtrate of a synthetic nonprotein culture medium in which tubercle bacilli have been grown. Satisfactory preparations are commercially available in tablets containing 0 00002 mg (first test strength) and 0 005 mg (second test strength)

Parke Davis & Co packages for 10 20 100 and 500 tests containing tablets and buffered diluent One tablet is dissolved in 1 cc of sterile diluent

Sharp & Dohme Inc packages of 1 10 100 and 250 vacule ampule vials (Lyovac) containing tablets and buffered diluent.

3 Tuberculin Patch Test. Filter paper is saturated with undiluted old tuberculin Koch. A satisfactory preparation is available from

Lederle Laboratories Inc cellophane wrapped assembled adhesive strip two tests and one control test (saturated with concentrated uninoculated broth)

Methods—For ordinary testing 0 1 cc of OTK 1 10 000 is injected intracutaneously and if the reaction is negative the 1 1 000 dilution is used or PPD Dose 1 is given and if reaction is negative Dose 2 dilution is used The reactions are read at 48–72 hours Whenever possible a control test should be performed preferably using the blank uninoculated sterile broth

In the patch test the strip is applied to an area over the sternal region or back or on the flexor aspect of the forearm The site is first cleansed with the acetone The strip is applied under pressure with the warm palm of the hand and is removed at 48 hours The test is read at 72–96 hours

For quantitative testing serial dilutions of OTK are prepared with normal saline or distilled water Table 24 shows the series of dilutions most in use All the higher dilutions (range of hyperergic reaction) must be *freshly prepared* at least every two weeks *All*

TABLE 24—DILUTIONS FOR QUANTITATIVE INTRACUTANEOUS TESTING TO ASCERTAIN LEVEL OF TUBERCULIN SENSITIVITY

Dilution	Range of Reaction
Undiluted	
1 10	Hypoergic
1 100	
1 500	
1 1 000	Normergic (usual adult sensitivity)
1 5 000 Median Normal Adult Sensitivity	
1 10 000	
1 100 000	Hyperergic
1 500 000	
1 1 000 000	

Dosage for each dilution is 0 1 cc OTK, injected intracutaneously

solutions should be kept in the refrigerator The dilutions representing the range of usual adult sensitivity give the approximate level at which most normal adults begin to react to an injection of 0 1 cc of OTK Individuals who *fail* to react even to the 1 500 1 100 and 1 10 concentrations are classified as distinctly *hypoergic* or relatively anergic individuals who commence to react to dilutions of 1 100 000 1 500 000 or 1 1 000 000 are classified as *hyperergic* Persons who commence to react to any of the three median concentrations (1 1 000 1 5 000 1 10 000) and cease at one or two dilutions below may be regarded as within the *normergic* range

The injections are performed as described in common technics (p 44) and are usually made into the skin of the upper arm or back The dilutions are placed 1½–2 in apart in a vertical column The position of each site is carefully marked with strips of adhesive or with indelible dye or ink, and an appropriate number is provided to facilitate identification. Readings of the inflammatory response are usually most significant at 48–72 hours after the injection.

It is best always to start with the lowest concentrations and to inject *only the four highest dilutions at the first testing* (those be

low the median in Table 24) Then if there are no reactions to any of these the three next higher concentrations can be injected the next day This reduces the risks which would be incurred were the greater concentrations administered to highly hypersensitive subjects (See contraindications and dangers)

According to the laws of statistical probability hyperergic normergic or hypoergic reaction to tuberculin each speaks somewhat in favor of the diagnosis of a disease in the respective category The known hyperergic normergic and hypoergic conditions and their salient characteristics are presented in Table 25

Evaluation of Positive and Negative Responses—True negative results to tuberculin tests are obtained

1 In persons never infected with tubercle bacilli

2 During the incubation period of infection before skin sensitivity has developed

3 In cachectic and moribund individuals (negative anergy)

4 Sometimes in measles whooping cough spinal or tuberculous meningitis (negative anergy etc)

5 *In persons with a disease characterized by a high degree of* hypoergy or anergy (sarcoids etc)

Other negative results may be due to faulty materials and technic

False positive reactions are obtained

1 When infected or other faulty materials are used

2 When there is allergy to substances in tuberculin other than those allergens originating from the bacillus

3 When the reaction is not an inflammatory response to tuberculin is instead an activation of some other form of cutaneous lesion

Contraindications and Dangers—Tuberculin tests should never be performed unnecessarily for they carry the unavoidable dangers of (1) focal activation and dissemination of dormant tuberculous processes (local exacerbation flare-up or extension of original focus hematogenous or lymphogenous dissemination, flare up or elicitation of tuberculids *etc*), (2) systemic reactions (3) excessive local re

action with the site of injection possibly even developing extensive necrosis. These dangers can be reduced to a minimum by *testing with serial dilutions, using only the greater dilutions as a first test* and proceeding to higher concentrations only when there has been no reaction to the smaller doses

TABLE 25—CLASSIFICATION OF COMMON TUBERCULODERMS ACCORDING TO IMMUNOLOGIC CRITERIA (LEVEL OF SENSITIVITY TO OT*)

Name	Histologic Structure	Demonstration of Bacilli	Tuberculin Reaction (Determined by Quantitative Intracutaneous Testing)
	I. HYPERERGIC FORMS		
Tuberculous chancre	First banal inflammation later tuberculoid	+ + +	First negative later hyperergic
Tuberculosis luposa (lupus vulgaris)	Tuberculoid (usually no central caseation)	+ + (Usually only demonstrable by means of animal inoculation)	Strongly hyperergic
Tuberculosis verrucosa cutis	Tuberculoid mixed with banal inflammation (no caseation but sometimes suppuration)	+ +	Hyperergic
Tuberculosis colliquativa (scrofuloderma)	Tuberculoid with a large amount of banal inflammation and suppuration	+ + +	Strongly hyperergic
Tuberculosis lichenoides (lichen scrofulosorum)	Tuberculoid	+ (In very early lesions) difficult to demonstrate particularly in fully developed lesions	Strongly hyperergic
Rosacea like tuberculid	Occasionally tuberculoid	Not accomplished	In some cases strongly hyperergic

Positive even at 1 1 000 000 1 500 000 or 1 100 000

TABLE 25 —CONTINUED

Name	Histologic Structure	Demonstration of Bacilli	Tuberculin Reaction (Determined by Quantitative Intracutaneous Testing)
	II TRANSITIONAL FORMS†		
Tuberculosis papulonecrotica	Tuberculoid but with many areas of banal inflammation and necrosis	Very difficult	Many cases hypoergic some strongly hyperergic others normergic
Tuberculosis indurativa (erythema induratum Bazin)	Tuberculoid but with many areas of banal inflammation and necrosis perivasculitis	Very difficult	Many cases hypoergic some strongly hyperergic others normergic
Lupus miliaris *disseminatus* faciei	Fully developed tubercles	Extremely difficult or im*possible*	Usually hypoergic some cases strongly *hyperergic* others normergic
	III HYPOERGIC AND/OR ANERGIC FORMS		
Sarcoidosis sarcoid of Boeck sarcoid of Darier-Roussy§	Tuberculoid (epithelioid)	Extremely difficult or impossible	Usually hypoergic
Miliary tuberculosis of the skin	Acute inflammatory reaction sometimes tuberculoid	+ + + +	Anergic or hypoergic

† In this group of tuberculoderms a relatively large number of cases show reduced sensitivity (an approach to anergy) whereas some are strongly hypersensitive and others have a normal degree of sensitivity

‡ Positive only in 1:100, 1:10 or undiluted

§ These and other hypoergic conditions such as granuloma annulare Hodgkin's disease and mycosis fungoides are not of proved tuberculous etiology

TREATMENT

No available immunologic or specific measure is of general value Nevertheless the level of skin sensitivity can usually be changed

and can often be *lowered* by repeated intracutaneous injections of tuberculin and in some tuberculoderms and even in other forms of tuberculosis some beneficial effect has been reported (e g tuberculin hyposensitization is reputed to be of use in ophthalmologic conditions) Almost all investigators agree however that the effects of tuberculin hyposensitization are *irregular* and the level of skin sensitivity which was originally present tends to become re established when the tuberculin injections cease

Most authorities agree that whatever beneficial effects may be achieved by methods of specific hyposensitization are often offset by the *risks of increasing* the tuberculin sensitivity and of activating or disseminating the tuberculous processes The present standard treatment of tuberculoderms therefore consists in nonspecific general measures e g high doses of calcium and irradiated sterol (calciferol) and local treatment or destruction But just as in prophylaxis the hope appears warranted that effective specific immunologic methods of treatment may some day be developed

IMMUNITY

Promising results have been obtained with BCG which is now widely used abroad However owing to the relatively favorable epidemiologic situation in this country no general use has been made here of this method

There is proof that *relative degrees of clinical resistance follow natural exposures* The development of adequate local resistance is apparent in the fact that on the first inoculation with tubercle bacilli there is usually spontaneous healing the site becoming scarred and quiescent Subsequent to this a certain degree of long lasting generalized resistance appears to be the rule Thus *most super or reinfections with tubercle bacilli do not lead to active or progressive disease* Effectiveness of resistance apparently varies from one environment to another with diet (e g vitamin D) from strain to strain family to family individual to individual and from time to time in the same individual Moreover this resistance seems to be in delicate balance in most persons and may on occasion be

broken down by any number of circumstances—massive or repeated exposures or contributory or trigger mechanisms such as intercurrent infections, ultraviolet light trauma dietary deficiencies other de bilitating factors etc

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Tuberculoderms do not generally present special public health problems and most patients with tuberculoderms do not represent hazards to persons in their environment Many forms of skin tuber culosis harbor few if any bacilli which can be transmitted (Table 25) In addition, those forms that harbor bacilli in the tissues are often closed lesions (lupus vulgaris etc) and there is no propul sion of large numbers of micro organisms into the environment as in coughing or spitting

On the other hand there is some risk of infection in children by direct contact with open and ulcerated forms rich in virulent bacilli (Table 25) When a case of open tuberculosis of the skin is dis covered young children and particularly infants should be kept from intimate contact with the patient and the objects he uses As a rule the children who *still have entirely negative reactions to tuber culin skin tests* are probably those *in the greatest danger* of serious infection but repeated reinfections in young children are also potentially dangerous

It is surely not necessary here to stress that tuberculous ulcers or other forms of tuberculosis of the skin particularly when located near body orifices should *lead to a search for active and open tuber culous foci in other organs and in persons of the patient's environ ment* In this respect all tuberculosis of the skin has a certain epi demiologic significance

Urticaria (Hives, Including "Giant Hives")

Both the morphologic entity called urticaria and the isolated lesion called urtica or wheal *can be elicited* by any one or any com bination of a great number of widely different eliciting factors Thus

some urticarias are elicited by infections (virus fungous bacterial) or infestations (intestinal and other parasites mites lice etc) and some by physical agents (stroking heat cold etc) In some in stances the eliciting factors may even be normal or abnormal body substances (hormones tissue metabolites etc) Some physi cians today believe that nervous influences and vasomotor disturb-ances may in and of themselves sometimes suffice to elicit hives but we have never discovered an authentic case of this sort. In addi tion to those in which eliciting agents and mechanisms can be de scribed or discovered there remains the *large group of urticarias of unknown causation*

Acute urticarial eruptions are exceedingly common and are generally *self limited* disappearing in several days to a few weeks Both the dis covery of the eliciting agent and the management generally present no particular difficulties in these acute cases

Conditions are sadly different in the less common *chronic* forms i e those in patients who continue to have hives for periods of six weeks up to many years with only short periods of freedom from the eruption In these cases too the eliciting factors and the basic mechanisms can sometimes be discovered, but more often than not both discovery of eliciting agents and causal management of the case present problems insoluble with our present knowledge

Among the pathogenic mechanisms which form the basis of urticaria the *allergic or immunologic* one undoubtedly often plays an important role In many (not all) *acute* cases and in a much smaller percentage of chronic ones it can be shown that the urti carial attacks follow exposures to one or more allergens to which the patient may have been specifically sensitized Of course even in these the exposure to allergen is usually not the sole factor but just one link in the chain of influences required to bring on the urticarial eruption

The following discussion deals with those forms of urticaria in which allergic or immunologic mechanisms play a discernible role However many of the special aspects pertaining to urticarias elicited

by *drug allergens* and those attributable to so-called '*physical allergy*' are dealt with in the sections on drug eruptions and physical allergies

PERIOD OF REFRACTORINESS TO SENSITIZATION

Urticarial sensitization can begin to develop immediately on exposure to an allergen But individuals may also remain immune or refractory to sensitization for variable periods of exposure before sensitization finally begins

INCUBATION PERIOD OF SENSITIZATION

In many cases this is not ascertainable when it is for example in urticarial sensitizations to certain drugs or insect bites the incubation period generally falls within the usual 6–28 days

REACTION TIME OF SENSITIVITY

When a patient with established acquired urticarial sensitivity i e, whose tissues have been sensitized by previous exposure encounters the eliciting allergen in an adequate manner the clinical reaction may occur within the first seconds or minutes or may take several hours or only rarely several days

The *clinical* reaction to a single exposure to allergen may last for hours for days and in some cases even for four to eight weeks However the wheal reaction to an allergen applied as a scratch or intracutaneous *skin test* generally appears within a few minutes and subsides in about one to two hours

PROPHYLAXIS

The accepted methods of avoidance and reduction of exposure to eliciting ingested inhaled or contacted allergens are by far the most important of immunologic measures and indeed, the only effective prophylaxis other than the now extremely valuable use of antihistaminic drugs (Pyribenzamine or Benadryl) *Hyposensitization with specific extracts is generally of no value in urticaria*

In all atopic persons with urticaria, the *utmost caution* must be observed in the administration of certain drugs (salicylates) and of foreign serums For in *atopic individuals there is considerably more*

than the usual danger of severe or even fatal reactions from these allergens

In addition to avoidance of specific allergens a most important part of prophylaxis consists in the avoidance and reduction of those contributory and trigger factors which often play a role in the inception and exacerbations of urticaria Among these are (1) friction—urticarial lesions are often localized or most severe in areas of pressure and/or friction (belt garters etc) (2) rapid or marked temperature changes (3) exertion (4) emotional and autonomic nervous system influences (e g blushing due to emotional factors flushing from rapid changes of temperature or ingestion of hot spicy foods liquor coffee tea etc)

DIAGNOSIS

SCRATCH OR INTRACUTANEOUS TESTS FOR DISCOVERING ELICITING AGENTS —Scratch tests and intracutaneous tests are generally of little or no value in the discovery of eliciting agents in urticaria In many patients with urticaria the presence of dermographism or urticaria factitia precludes the proper execution and evaluation of skin tests for wheal reaction In many other persons with urticaria *skin tests will produce wheal reactions with allergens which can be shown to be of little or no clinical importance* (avoidance of the skin test positive allergen will often fail to produce improvement or remission and re exposure of the patient to that allergen will often fail to produce an exacerbation or recurrence) Conversely *allergens of proved clinical importance* i e those shown to produce exacerbations of the urticaria *may fail to elicit wheal reactions on skin test*

For these reasons in most cases of urticaria *skin tests need not be performed* They are generally valueless except for legal or research reasons or perhaps as a last resort when the history specific eliminations and all nonspecific measures have failed

The following directions apply to those exceptional cases in which the physician feels he *must* have recourse to skin tests

Materials—As in most allergic diseases in chronic urticaria the choice of materials for skin testing is based on a general knowledge of the situations in which exposures to the eliciting allergens are likely to occur and on the individual history and course of the particular eruption

1 Selection Based on History The suggested line of questioning is given in Chapter 1 The physician seeks his clues in the onset, past exacerbations and remissions endeavoring to relate these to exposures and avoidance of exposures to certain urticariogenic allergens

2 Selection Based on Course of Eruption and Results of Avoidance and Re-exposure Here the course of the eruption and in particular the effects of natural and deliberate avoidance and re exposure to suspected allergens are used as guides

3 Selection Based on Localization of Eruption In most cases of urticaria the allergens are disseminated via the blood stream and the *sites* of the lesions are of *no* help in tracing the eliciting agents However in some patients urticaria is produced by allergens which penetrate the skin from without. In these the sites of origin (or of maximal development) of the eruption provide valuable clues to possible eliciting agents (The *common localization of urticarial lesions in areas subjected to stasis friction and/or pressure* such as under the belt hatband garters etc *must never be erroneously attributed to the local urticariogenic effect of external contact with allergens*)

In rare instances the physician may deem it advisable to perform skin tests with the substances recognized as the most common eliciting protein allergens in urticaria even without previous evidence against a particular allergen. In such cases the routine series of allergens given on page 211 may be used

Application of Tests—Many of the materials for scratch testing and some for intracutaneous testing can be obtained commercially (p 212) Materials for scratch and intracutaneous testing which are not commercially available must be prepared in such manner concentrations and vehicles as to exclude primary urticariogenic

effects as well as other damage either local or systemic Directions for preparation and technic of use of such materials and the pre cautions to be taken are given in Chapter 1

Readings and Evaluation of Reactions—Readings are made at 10–30 minutes and results evaluated as described on page 34

Contraindications and Dangers—Contraindications and dangers are described on pages 35 and 41

TRIAL AND ERROR TESTS TO DISCOVER ELICITING AGENTS—In contrast to the usually negligible value of skin tests *clinical tests* of avoidance and/or reduction of exposure and re exposure to allergens are of great value in many cases of allergic urticaria

Elimination procedures are easiest to perform in *acute* urticaria in which the sudden onset and the short duration frequently point to the eliciting agent even without any test. Unfortunately in subacute or *chronic* urticaria in which information concerning eliciting agents is most needed exacerbations and remissions are part of the normal course of the eruption and the evaluation of effects of avoidance and re-exposure is often beset with the greatest difficulties

In our experience in most long standing urticarias it is impossible to ascertain the effects of deliberate avoidance and exposure to allergens because of these normal spontaneous fluctuations and remissions of the eruption Moreover in cases of multiple causation i.e in cases with more than one eliciting allergen or with allergens plus other factors as causes the evaluation of exposures and flare ups is usually difficult and often unsuccessful

Selection of Allergens—The allergens for avoidance and re ex posure tests are selected in about the same manner as are the allergens for skin testing

1 On the basis of the *history and clinical* course i e by observ ing the chronologic relationships between certain allergenic ex posures and onset or exacerbation of the dermatosis and between reduction of certain allergenic exposures and improvement of the dermatosis

2 On the basis of experience and knowledge which has shown that particular materials are notorious eliciting agents of allergic urticaria The following examples are typical of such urticariogenic allergens [9]

Foods shellfish, fish (including caviar) strawberries cheese nuts eggs, wheat, milk, pork, chocolate (and their derivatives and products)

Inhalants feathers orris lycopodium rice and starch powders animal danders human dander (?) house dust and other forms of dust (including kapok, cotton silk wool tobacco fungi flaxseed oil, Karaya gum pollens plants and flowers insecticides dyes and dyed materials of all kinds etc)

Drugs (see also section on drug eruptions) salicylates barbiturates sulfonamides penicillin, iodides bromides quinine ipecac, the opium group phenolphthalein the belladonna group etc.

Allergenic products of living agents micro-organisms etc

Foci of infection particularly of teeth tonsils sinuses gallbladder and bowels

Infestations particularly insects gastrointestinal parasites trichinae filariae etc

Avoidance of each suspected allergen should be carried out for *at least one week* There is usually some degree of improvement within this period if the allergen is of clinical importance However in *exceptional cases of subacute and chronic urticaria* and in some cases of *angioneurotic edema* avoidance of each suspected allergen should be carried out for *at least four weeks* and preferably *eight weeks* It sometimes takes several weeks after avoidance of an offending allergen for these patients to show improvement

Re exposure to an allergen which is of clinical importance usually leads to an exacerbation or recurrence within a few minutes to one or two days

For directions for the technic of *avoidance and re exposure tests* see page 59 for foods page 58 for inhalant allergens and page

[9]Urticariogenic allergens can act after gastrointestinal respiratory or other absorption and dissemination to the skin or they can on occasion contact the skin from without, penetrate the epidermis and cause local and/or distant hives

66 for drugs In performing avoidance and re-exposure tests the patient should always be instructed in the measures to be taken in case severe immediate reactions result from trial exposures

1. In most cases of *acute* allergic urticaria, well directed observation and common sense deductions on the part of the physician and/or the patient will lead to discovery of the eliciting allergens
2. In most cases of *chronic* urticaria the mechanism and the eliciting agents both remain *unknown* and prevention and treatment are *unsatisfactory*
3. *Skin tests* are generally of *no* value in discovering eliciting agents in urticaria of any type
4. Avoidance and re exposure tests with logically chosen allergens may be of great value in discovering eliciting agents in selected cases of urticaria
5. If the results of avoidance and re exposure tests are in disagreement with the results of skin tests the evidence furnished by the former is conclusive
6. In those cases of *chronic* urticaria in which causes can be found *drugs* (salicylates iodides bromides etc) and *foci of infection* (teeth tonsils etc) are by far the commonest
7. Adjuvant or synergistic influences including emotional upsets fatigue physical influences (temperature friction) endocrine and dietary abnormalities underlying other disease (blood dyscrasias diabetes endocrine abnormalities hepatic or kidney disease etc) may play a role in some cases of urticaria. Such contributory factors should be sought and eliminated or reduced in all chronic and resistant cases (See text books on dermatologic therapy)

TREATMENT

IMMUNOLOGIC MEASURES—*Hyposensitization* with specific extracts is generally *ineffective* in urticaria

Avoidance of exposure to the offending allergen or allergens is the best and generally the only effective, immunologic treatment. *Reduction* of exposure is sufficient to bring relief to some patients and should always be attempted when complete avoidance of exposure is not feasible

NONIMMUNOLOGIC MEASURES—The following nonimmunologic or nonspecific measures usually do no harm and may perhaps in some cases increase the patient's tolerance to certain urticariogenic allergens

1 Antihistaminic agents Either Pyribenzamine (Ciba) or Benadryl (Parke Davis) in 25–50 mg doses by mouth three to four to eight times in every 24 hours *In our experience this has been by far the most valuable form of nonspecific therapy* and is more effective than any or all other measures in certain chronic urticarias and in angioneurotic edema *About 75 per cent of the cases improve* (Urine and blood examinations should be done once weekly while these drugs are being taken)

2 Solution of crude liver Injections of 5 cc *are given intramuscularly three times weekly* (or intravenously when suitable extracts are available)

3 Ascorbic acid Doses of 500–1 000 mg daily by mouth

4 Menadione (vitamin K) Doses of 2 mg three times daily before meals by mouth

5 Autohemotherapy From 10 to 20 cc of the patient's blood is drawn from the vein and at once injected deep intramuscularly into the buttock This treatment should be repeated twice *weekly or* every other day for a total of 6–8–10 injections

6 Thyroid extract (This should not be prescribed unless the basal metabolic rate is below normal or at a low normal level

and unless the patient can remain under regular periodic medical observation)

7 Histamine acid phosphate Injections of a solution containing 275 mg per 5 cc of distilled sterile water are given subcutaneously starting with 0 02 cc and increasing daily by 0 02 cc until a dose of 0 4 cc or 0 5 cc is reached At about this dose injections are usually followed by headaches That dosage at which headaches are produced is considered the maximal dose for the particular case As soon as this dosage is reached it is maintained without further increase Injections of the maintenance dose are given every other day for two weeks and then twice weekly over a long period

8 Routine avoidance of certain drugs and foods which are notorious for causing urticarial eruptions (salicylates barbiturates phenolphthalein iodides and bromides penicillin and chocolate nuts fish shellfish berries etc)

9 Measures to eliminate general medical conditions sometimes considered contributory are (*a*) elimination of foci of infection (teeth tonsils sinuses prostate etc) (*b*) treatment of liver and gallbladder disease kidney disease gastrointestinal disease diabetes mellitus endocrine disturbances intestinal parasitic infestation anemias blood dyscrasias psychogenic and emotional factors

IMMUNITY

Although most attacks of urticaria are self limited there is no evidence that *significant or lasting general hyposensitization or acquired specific immunity* is brought about either through natural or through deliberate hyposensitizing measures However in some patients temporary or permanent hyposensitization appears to occur spontaneously Moreover many patients will at certain times support with impunity exposures to foods inhalants or drugs which will at other times be followed by urticarial eruptions

Temporary local refractoriness to whealing is a regular occurrence after skin sites have undergone an urticarial response This refractoriness is probably not immunologic or specific.

Verruca Plana, Verruca Vulgaris (Common Wart, Plantar Wart, "Papilloma")

INCUBATION PERIOD
Probably weeks to months to *years*

PROPHYLAXIS
No immunologic method available

DIAGNOSIS
No immunologic method available

TREATMENT
The value of active immunization with sterile "wart vaccine" prepared from macerated wart tissue in saline suspension is not generally accepted but is supported by convincing studies of reliable investigators. Unfortunately the method cannot be checked by general clinical trial for the vaccine is not commercially available.

Zoster (Herpes Zoster, Shingles)

INCUBATION PERIOD
Probably 3–14 days

PROPHYLAXIS, DIAGNOSIS AND TREATMENT
No immunologic methods available

IMMUNITY
Some observers believe herpes zoster to be a partially immune localized form of chickenpox or at least to be closely related to chickenpox.

One attack of herpes zoster appears to produce long lasting or permanent immunity. In contrast to herpes simplex recurrent attacks of zoster are extremely rare or nonexistent. (It is possible that some cases reported as *recurrent herpes zoster* are not true zoster but *recurrent herpes simplex localized along the course of cutaneous nerves* [*herpes simplex zosteriformis*].)

Chapter Seven

IMMUNOLOGIC MANAGEMENT OF SPIDER, INSECT AND SNAKE BITES

Marion B Sulzberger, Rudolf L Baer, Abram Kanof and Naomi M Kanof

INCLUDED AMONG the mechanisms through which different species of biting animals effect damage in man are (1) poisoning (by toxins etc.) (2) sensitization by allergenic products and (3) a combination of these two The following discussion deals only with those types of damage for which immunologic diagnostic and/or therapeutic procedures are available

Black Widow Spider Bites

INCUBATION PERIOD
None

PRODROMAL SYMPTOMS
None

PROPHYLAXIS
None

DIAGNOSIS
No immunologic method available

TREATMENT

Indications —Although the incidence of fatalities resulting from the bite of the black widow spider (Latrodectus mactans) is low the severity of the toxemia (nausea sweating intense abdominal pain tremors etc) warrants the use of *antivenin* therapy as soon as evidence of the bite (swelling pain purpura) is observed This form of treatment should of course be used in addition to nonimmunologic measures

Material —Black Widow Spider Antivenin is manufactured by Sharp & Dohme Inc package includes one Vacule vial to yield 2 5 cc restored double concentrated serum, one 2 5 cc vial of pyrogen free sterile distilled water and one 1 cc. vial of normal horse serum (diluted 1 10) for use as test and desensitizing material

Method —A dose of 2 5 cc antivenin is administered *intramuscularly* immediately on establishing the diagnosis This dose is repeated in one to three hours if the symptoms have not been relieved

Contraindications —The usual precautions against accidents caused by hypersensitivity to horse serum must be observed

Insect Bites and Reactions to Skin Parasites

It is today recognized that many of the skin reactions to the bites of common insects and parasites are due to *specific cutaneous sensitization* to the products of the insect rather than to primary irritant substances or toxins Thus the usual whealing and itching following mosquito bites the itching and eruptions from bites of *lice* and *bedbugs* and *fleas* and even the itching and eruption of *scabies* have been proved to be based largely on the host s specific acquired immunologic changes (i e on his allergic sensitivity to substances derived from the parasite) However immunologic or hyposensitizing measures have not yet been generally adopted to treat or to prevent the normal responses to insect bites Only in selected cases of *excessive* responses have hyposensitization procedures proved their value

INCUBATION PERIOD

Unless the individual is refractory to sensitization a specific cutaneous sensitization will develop probably from six days to several weeks after the first bite or exposure to the specific insect allergen

PROPHYLAXIS

Indications—Hyposensitization with extracts made from the insects is of considerable value in the following conditions produced by insect bites

a) Severe immediate urticarial reactions at the site of the bite

b) Urticaria asthma coryza from absorption of allergenic material from the site of the bite

c) Perhaps in some persons with excessive or abnormal 24–48 hour tuberculin type hypersensitivity to insect bites

Material—No insect extracts are marketed at present Until recently extracts of bee housefly mosquito sand fly and wasp were commercially available in strengths containing 0 001 mg N per cc and 1 mg N per cc.

Method—When insect extracts are available the following schedule is used If the intracutaneous test with the extract containing 0 001 mg N per cc results in a wheal of not more than ½ in in its longest diameter the first dose may be 0 1 cc of this strength extract *subcutaneously* followed by 0 2 0 3 0 5 0 7 and 1 cc doses at weekly intervals Injections are then continued at weekly intervals with a 1 100 dilution of the extract containing 1 mg N per cc (dilution containing 0 01 mg N per cc) giving 0 1 0 2 0 3 0 5 0 7 and 1 cc *subcutaneously* finally weekly injections of a 1 10 dilution (0 1 mg N per cc) are given in 0 1 0 2 0 3 0 5 0 7 and 1 cc doses *subcutaneously* In some patients injections of the undiluted 1 mg N per cc extract may be required to produce maximal protection Dilutions are prepared with the diluting fluid furnished

The tuberculin type reaction to insect bites is often associated with the urticarial type of hypersensitivity to insect extract allergens

Hyposensitization to this form of reaction can probably also be achieved by the procedures outlined

Contraindications and Dangers—Hyposensitization with insect extracts appears to be a generally safe prophylactic procedure However experience with hyposensitization to insect bites is still limited and caution is advisable Dosage and length of treatment must be carefully adjusted according to the patient's response to injections After severe local reactions or a systemic reaction the next dose should be no more than 1/100 of the dose which caused the reaction

DIAGNOSIS

SKIN TESTS —*Indications*—Skin tests with insect extracts are generally of considerable value in confirming clinical suspicion of *hypersensitivity* i.e., *unusual* or *excessive* response of a particular patient to the allergenic products and bites of a particular species of insect

Material—Insect extracts for diagnosis are not at present commercially available

Methods—If insect extracts are available the following tests may be performed (1) For immediate urticarial reaction *scratch tests* with insect extracts are performed usually on the flexor aspect of the forearm or arm with a control test on a symmetrically placed area on the other arm (2) For 24–48 hour tuberculin type reaction an *intracutaneous* injection of 0 1 cc of insect extract containing 0 001 mg N per cc is given

Time and Method of Reading Test—(1) Early urticarial reaction is read at 15–30 minutes (2) The 24–48 hour tuberculin type reaction is read at 24–48–72 hours

Description and Evaluation of Reaction—1 Immediate urticarial reactions usually appear in 1–10 minutes and persist for 20–60 minutes The response is indicated by a wheal (sometimes with pseudopods) and surrounding erythema (wheal 1 cm or more in diameter) The test should be considered positive only if the reaction

at the site tested with insect extract is definitely larger than that at the control site

A *positive* reaction demonstrates that the person has an urticarial type of *hyper*sensitivity to the particular extract. Hyposensitization is indicated if there are severe clinical manifestations based on an urticarial form of hypersensitivity such as asthma hives or coryza A *negative* reaction shows that the individual has not developed a de monstrable urticarial hypersensitivity to the particular insect extract tested.

2 The 24–48 hour tuberculin type reaction appears at 24–48 hours and persists usually for two to four days or longer Response is indicated by an area of erythema a papule or induration and edema (about 1–3 cm in diameter) In some instances a vesicle may develop in the center of the reaction

A *positive* reaction indicates that the individual has developed a tuberculin type *hyper*sensitivity to the particular insect extract. (This form of sensitization is in most cases associated with an urticarial type of sensitization) A *negative* result indicates that the person has not developed a tuberculin type *hyper*sensitivity to the particular insect extract

Contraindications—Skin tests with insect extracts are generally a safe diagnostic procedure In patients with extreme clinical sensi tivity to a suspected insect extract the directions given on page 93 should be adhered to carefully

TREATMENT

In persons with manifestations of hypersensitivity to insect bites hyposensitization outlined under prophylaxis can be instituted as treatment even during periods of clinical exposures

IMMUNITY

NATURAL—Many individuals possess an absolute or relative temporary or permanent degree of protection against the bites of one or several species of insects This may consist of *refractoriness* to sensitization may be due to *acquired hyposensitivity* or *anergy* to in

sect allergens may be an immunity to insect *poisons* or *toxins*[1] or may be a combination of these

ACQUIRED —Active hyposensitization is feasible in some cases Moreover in some persons repeated insect bites probably produce temporary or permanent active immunization to toxins and perhaps also produce hyposensitization to insect allergens

Snake Bites

INCUBATION PERIOD

None

PRODROMAL SYMPTOMS

None

PROPHYLAXIS

No immunologic method available

DIAGNOSIS

No immunologic method available

TREATMENT

Indications —Immediate administration of antitoxin is indicated in all venomous snake bites

Materials —A complete individual Compak Suction Snake Bite Outfit is supplied by Cutter Laboratories for the first aid treatment of poisonous snake bites This contains lymph constrictor lancet two suction cups antiseptic and complete directions An advantage is that it permits the patient to remain ambulatory while continuous treatment is maintained

Antitoxin i e antivenin, prepared by immunizing animals—usually horses or mules—is generally accepted as therapeutically valuable

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[1] It has been stated that not all reactions from insects are caused by sensitizing allergens There are many species of insects which apparently secrete primary irritants or toxins that elicit skin lesions In some persons specific immunity to these insect poisons can be acquired or produced (e g immunity to bee poison) Other species of insects possess both poisons and sensitizing allergens Here again combined immunization to the insect poisons and hyposensitization to the insect's sensitizing allergens can occur

North American Anti Snake Bite Serum—Antivenin (Nearctic Crotalidae)—is a combined serum against rattlesnake and moccasin venom and is the only one generally available in this country

Sharp & Dohme Inc. package includes "Vacule ampule vial to yield 15 cc. of restored serum, 15 cc. syringe of pyrogen free, sterile distilled water for a diluent and 1 cc vial of 1 10 dilution of normal horse serum for use as test and desensitizing material

Method—In an early case (within 1–2 hours) small subcutaneous injections of 2–3 cc should be given locally to minimize local tissue destruction. In late cases this is probably of no advantage Following the local injection the remainder of the serum is given *intramuscularly* or *subcutaneously* Observe the patient carefully if symptoms do not subside in four hours repeat the injection. Four injections (totaling 60 cc) may be necessary Children require larger doses than do adults for in proportion to their weight they receive a greater concentration of venom from the snake bite

Contraindications—The usual precautions against accidents caused by hypersensitivity to horse serum must be observed Administration of antivenin should never interfere with the execution of other therapeutic measures such as local antisepsis incision and suction

EPIDEMIOLOGY AND PUBLIC HEALTH ASPECTS

Proper protective clothing should be worn in snake ridden country Since children incur a large percentage of snake bites they should be instructed to report at once any such occurrence Community protection may be attained by systematic killing of venomous snakes

Chapter Eight

MISCELLANEOUS ALLERGIES

W C Spain

Allergic Disturbances of the Eye

ALLERGIC DISTURBANCES of the eye rarely occur alone They are usually associated with major clinical conditions such as the respiratory allergies (perennial allergic coryza hay fever and bronchial asthma) the allergic dermatoses (atopic or nonatopic) and the gastrointestinal allergies The eliciting agents of importance in the major clinical conditions (i e the air borne inhalants foods drugs and the products of micro-organisms) are of equal importance in the causation of allergic conditions of the eye

These eliciting agents may be absorbed by direct contact with the intact tissues of the eye such as the lids conjunctiva and cornea or may be transported to these areas by the blood or lymph channels after entry into the body by ingestion by inhalation by injection procedures (as after overdoses of pollen extract) by absorption of the products of micro-organisms from an infective focus and by other routes

THE LIDS —The lids frequently are the site of an eczematous contact type dermatitis This manifestation of allergy was fully cov

ered in the section on eczematous contact type dermatitis (p 29))

The lids may also be involved in an acute or chronic recurrent urticarial type of response such as that described under urticaria or in lichenified and eczematous changes of the atopic dermatoses Such responses in the lids are characterized by itching and erythema edema and supervening chronic changes and are caused by direct contact with the air borne inhalant group of excitants—pollens dusts animal danders vegetable powders such as orris—or by direct contact with or ingestion of foods or drugs These groups of allergens have been described as being of major importance in the causation of bronchial asthma (p 202) urticaria (p 380) and atopic dermatoses (p 263)

Drugs by ingestion are but occasional causes (The role of arsenicals mercury penicillin the sulfonamides phenolphthalein and the salicylates is discussed on page 278) Infections of the teeth tonsils and paranasal sinuses may initiate acute or chronic allergic reactions of the lids Although little definite is known it appears probable that inhaled drugs and other allergens entering the nasal mucosa may cause allergic reactions of the eyes and lids

THE CONJUNCTIVA.—The forms of allergic involvement of the conjunctiva are similar to those of the lids and are often associated with them They consist of the eczematous contact type dermatitis and the acute edematous and the chronic recurrent types of reaction The modes of contact and the causes are similar to those of allergic conditions of the lids

It is probable that allergic reactions are a common basis of the condition known as *vernal catarrh* Occasionally inhalants especially fungi and pollens seem implicated both by the history and by the scratch or intracutaneous test for wheal reactions *In the majority of cases however skin tests fail to elicit positive reactions and the season of occurrence fails to coincide closely with any pollen period or combination of pollen periods* Despite the seasonal occurrence of most cases of vernal catarrh *chronic infections of the upper respiratory tract* especially of the teeth tonsils and sinuses

TABLE 26—MISCELLANEOUS ALLERGIC ENTITIES: SKIN TESTS AND IMMUNOLOGIC PROCEDURES IN PROPHYLAXIS AND THERAPY

CLINICAL ENTITY	SKIN TEST		PROPHYLAXIS		SPECIFIC THERAPY	
	Type	Value	Type	Value	Type	Value
Allergic disturbances of the eye	Scratch or intracutaneous tests with inhaled, ingested or contacted *allergens* read in 5–20 min. Response: wheal and flare	Generally of value	Avoidance of and protection against inhaled, ingested and *contacted allerg*	Generally of value	Avoidance of and protection against proved inhaled, ingested and contacted causal *allergens* plus hyposensitization with specific extracts	Generally of value
Gastro-intestinal allergy. Allergic headache	Scratch or intracutaneous tests with suspected ingested allergens read in 5–20 min. Response: wheal and flare	Of little value; foods proved positive clinically often fail to react on skin test and vice versa	Avoidance in the diet of substances proved causative	Generally of value	Avoidance in the diet of substances proved causative	Generally of value

Eczematous contact-type d m of h 1 d i tested nd rea ed ar o he form of co act d rm is

frequently seem to be concerned These conditions should always be suspected of being the possible source of a bacterial sensitization that results in vernal catarrh

CORNEAL REACTIONS—*Corneal ulcers* are at times considered allergic in origin with causes similar to those active in allergy of the conjunctiva. Inhalants foods and drugs by ingestion drugs and dyes by contact, as well as products of micro-organisms all must be con sidered possible eliciting agents Sometimes one or several of these factors act not as exclusive allergenic causes but as contributory or trigger factors activating bacterial or virus diseases of the cornea (*pneumococcic* or *herpetic keratitis* etc)

UVEAL TRACT—The pigmented vascular layers of the eye the iris the ciliary body and the choroid together form the uveal tract. In apparently rather rare instances these tissues singly or in any com bination may be involved in reactions of allergic origin.

There are many theories about the mechanisms of these reactions but only the following will be cited here A patient s own lens pro- tein altered by operation on the lens capsule by the formation of a cataract or by an infection is said to become allergenic and thus the cause of allergic cataract or uveitis Similarly a sympathetic uveitis may result from sensitization to *pigment* of an inflamed eye

As a rule a uveitis may be identified as allergic only when it is as sociated with more obvious clinical allergic conditions of respiratory intestinal or cutaneous type The eliciting factors found responsible in the major conditions then are usually also causes of the uveitis

OTHER ALLERGIC CONDITIONS OF THE EYE—Other diseases of the eye are at times recognized as allergic in character Optic neu ritis retinitis and cataract have occasionally been shown to result from sensitization to foods drugs or therapeutic serums The identification of an allergic origin for such conditions is usually difficult.

However it is exceedingly important for every physician to recall that *cataracts* are not an altogether infrequent occurrence in severe *atopic dermatitis* Whatever the basic mechanism of this form of

cataract it is obviously and unmistakably *a part* of the atopic dermatitis syndrome and one of its *most serious* manifestations For this reason every patient with atopic dermatitis requires regular ophthalmic examinations The serious results of such cataracts developing in children and adolescents are obvious and, of course the possibility of their development renders imperative early adequate treatment of atopic dermatitis

DIAGNOSIS

The diagnosis of allergy of the eye is established by history and by skin tests The testing materials indicated their sources and the contraindications and dangers of the tests have been described in the section on bronchial asthma (pp 210 ff) If the condition is an eczematous contact type dermatitis of the lids the procedure is that described on page 308 The diagnosis is often made possible only by the presence of an associated and more obvious form of clinical allergy

IMMUNOLOGIC TREATMENT

The methods of immunologic treatment of conditions of the eye usually are similar to those for the associated syndrome (See treatment for bronchial asthma p 215 atopic dermatoses p 269 contact type eczematous dermatitis p 334, drug eruptions, p 291) Hyposensitizing injections may be given using extracts of the pollens, fungi and nonseasonal inhalants which have been found positive by skin test and clinical history Foods drugs and any other allergens considered suspicious should be removed or avoided as far as possible Proper treatment of any proved upper respiratory infection should be obtained Since allergic eye conditions are usually present with other and major allergic conditions specific management and adequate treatment of the latter may often prove sufficient to clear the eye condition This is a particularly important guide to the treatment of that form of cataract which develops in atopic dermatitis. Further progress of the atopic disease in the lens is usually halted when the skin and general conditions are mastered.

Treatment of vernal catarrh is rarely successful by any method Injection therapy with the extracts of the pollens fungi or inhalants manipulation of the menu (diet) and eradication of any focus of infection should be attempted when there is sufficient indication

The treatment of the isolated allergic eye condition is rarely successful unless the eliciting agents can be discovered and removed When complete removal of causal allergens is impossible attempted hyposensitization with the injected extracts of the eliciting agents may prove helpful

Gastrointestinal Allergy

Like respiratory allergy gastrointestinal allergy designates the organs which react to allergenic substances not the class of allergens Thus gastrointestinal allergy is not synonymous with food allergy

Sensitization to food or food allergy may manifest itself in minor forms or in one or more of several major clinical forms such as respiratory cutaneous neural or gastrointestinal allergy For instance a patient may develop coryza and bronchial asthma following ingestion of foods to which he is sensitive In such cases the allergenic food substances penetrate the gastrointestinal membranes and are transported by the circulating blood to the sensitized tissues located in the nasal and bronchial areas Despite the close contact which naturally occurs between such absorbed foods and the intestinal tissues through which they pass no symptoms of gastrointestinal allergy need appear In other allergic patients however the gastrointestinal membranes do contain sensitized areas composed of shock tissue in which symptoms characteristic of *gastrointestinal allergy* develop on ingestion of the specific food substances

But gastrointestinal allergy although frequently caused by foods is not necessarily always due to this class of allergens Indeed a not too uncommon cause is a sensitiveness to drugs or to the products of micro-organisms

Attacks of colic in infants and stomach ache in children may be evidence of a gastrointestinal allergy to one or several of the more common foods Nausea vomiting diarrhea rashes or respiratory symptoms may occur concomitantly but frequently there are no *associated* allergic symptoms In older patients symptoms referable to associated allergic disturbances are usually found These may include coryza sneezing itching of eyes edema of the lids and conjunctivitis headache vertigo cough or bronchial asthma erythema purpura itching and eczematization of the skin urticaria and angioneurotic edema Many gastrointestinal allergies would go unrecognized were it not for these associated symptoms which often are more readily identified evidence of an allergic reaction

The vague obscure and nonspecific symptoms and signs of gastrointestinal sensitization frequently mimic the symptoms and signs of those urgent and nonallergic disorders that produce the "acute surgical abdomen (appendicitis gallbladder colic etc) The diagnosis of both acute and chronic gastrointestinal allergy is most difficult and often must be reached by the devious process of exclusion Clinical manifestations associated with gastrointestinal allergy may include edema of the tongue lips pharynx buccal mucosa canker sores or herpes, foul breath coated tongue flatulence nausea vomiting anorexia vertigo abdominal pain diarrhea constipation increased mucous secretion and colonic spasm pruritus ani There is often an accompanying lassitude

DISCOVERY OF ELICITING AGENTS

Many gastrointestinal reactions immediately follow the ingestion of the offending food but in other instances there may be an interval of 24–48 hours before symptoms appear In patients having delayed symptoms all forms of *skin tests with foods will usually be negative* and reliance must be placed on the investigation of dietary habits.

The foods most commonly at fault are NUTS SEAFOOD CHOCOLATE, EGG MILK WHEAT although *any food should* be a suspect. Ingested drugs including aspirin arsenic and mercury are occasional causes (p 208)

Patience care and conservative conclusions must be applied to the investigation of gastrointestinal allergy *Regardless of evidence by skin test by history and by other data the allergenic role of a food or drug must not be considered proved unless the symptoms and signs can be demonstrated not to be attributable to nonimmunologic forms of intolerance* (faulty digestion hyperacidity gallbladder disease etc) *and unless avoidance regularly produces relief from the allergic symptoms and re exposure regularly produces exacerbation or recurrence* Observance of this rule will show that cases of food allergy are *not as common* as it has been the fashion to believe

Methods—Attempts to discover eliciting agents may be by history by clinical tests of avoidance and re-exposure and if necessary by skin tests (see Chapter 1) *Specific causes* particularly those foods listed as causes of bronchial asthma (p 207) atopic dermatitis (p 265) and urticaria (p 386) should be considered.

Contraindications and Dangers—Extreme care must be taken in testing foods or drugs either cutaneously or clinically Pronounced sensitization frequently exists and serious consequences may result from exposure to an allergenic food The patient s history usually will indicate such extreme sensitivity and the foods involved should be avoided both in clinical exposures and in skin testing

TREATMENT

Avoidance or reduction of exposure to food or to other culpable allergens is the recommended therapy *Specific hyposensitizing injections and oral administration of the specific food or drugs are not advised*

In some patients *complete* avoidance of the offending foods is necessary to obtain freedom from symptoms In others *partial* avoidance is sufficient to reduce or to eliminate the symptoms A reappearance of symptoms will show that there has been a premature resumption of exposures to food or to other excitants After existing for months or years the hypersensitivity forming the basis of gastrointestinal allergy may *disappear spontaneously* In some patients this disappearance is sudden but in most it is gradual

Allergic Headache

Sensitization to food may manifest itself not only in gastrointestinal and other allergies but also in *headaches of allergic origin*. Such headaches may be typical migraines of brief duration but more commonly *are not* confined to one side of the cranium and are *not* associated with nausea, vomiting and ocular manifestations. Sometimes other allergic conditions such as coryza, asthma and cutaneous or gastrointestinal allergy may appear concomitantly.

Whereas *foods* by ingestion are usually the cause in cases with demonstrable etiology, occasionally other allergens are at fault. Thus headaches of a milder type may occur owing to nasal obstruction from the edema which results from inhalation of an air borne substance (pollens, animal danders, dusts). Occasionally the strong odor of a food such as celery or banana may produce such a headache.

Some cases of *migraine* are considered by many to be the manifestation of a more severe and more disabling form of allergic headache which is caused by a more overwhelming sensitivity to foods or less commonly to other allergens. In both milder allergic headaches and allergic migraine, the symptoms are thought to be caused by an *edema* occurring paroxysmally within the cortical areas.

DISCOVERY OF ELICITING AGENTS

As in gastrointestinal allergy, the search for eliciting agents by scratch or intracutaneous *skin tests* with food extracts is usually *successful only in those patients whose headaches develop immediately* or possibly within three to six hours after the ingestion of the food. When an interval of 24–48 hours elapses before the occurrence of the headache, skin tests are usually negative and other methods must be used (see clinical tests with foods, p. 59).

The foods most often culpable are those also most active in producing gastrointestinal allergy, namely nuts, seafood, chocolate, egg, milk and wheat.

Contraindications and Dangers.—Those described for gastrointestinal allergy apply here.

TREATMENT

There must be avoidance of the food or foods found guilty (see p 69) I have not found oral therapy with specific food materials to be helpful Injection therapy with specific food materials is contraindicated

Other Pathologic States Attributed to Allergy

According to present concepts the pathologic condition which develops in many forms of simple uncomplicated and acute allergic reactions *is a localized and temporary edema* Such edema results from the damage to and consequent increased permeability of the capillaries or other vessels in the tissue areas which have become sensitized i e have become specifically vulnerable to the absorbed allergenic substance whether it be an inhalant a food drug or a product of micro organisms The *site* of the *sensitized tissue* area is an important factor for it determines the clinical form assumed by the allergic response It is the congestion and edema of the part of the body involved that produces the embarrassment of function which in turn is responsible for the signs and symptoms characteristic of the particular allergic condition Such tissue edema usually occurs in the respiratory or gastrointestinal tract or in the skin It will occasionally occur in other areas—the auditory genitourinary cardiovascular or nervous system and the joints In addition to this acute edematous response many allergic reactions consist of more chronic changes such as inflammation cellular infiltration and later fibrosis

Most authorities today believe that the following pathologic states may occur as a result of localized allergic reactions in different sites

Vertigo tinnitus and Menière s syndrome may occasionally be based on an allergy to foods or to drugs

Urinary frequency renal and bladder pain and *hematuria* have been attributed at times to food or drug allergy

There is evidence indicating that *periarteritis nodosa and other vascular and connective tissue diseases* are in some way attributable to allergic reactions to foods drugs therapeutic serums and the prod

ucts of micro-organisms *Cardiac arrhythmias* seem at times to be of allergic origin *Paroxysmal tachycardia and extrasystoles* may be the result of food or drug sensitization In addition many other diseases of the cardiovascular system including the veins and venules may be connected with allergic reactions

Allergic purpura thrombocytopenic purpura and thrombocytopenia leukopenias agranulocytosis and *aplastic anemias* are among the blood dyscrasias which have been attributed to allergic responses to foods to drugs and to bacterial products It is quite possible that certain cases of *leukemias* and other malignant proliferations may be connected with allergic reactions *Loeffler's syndrome (eosinophilic bronchiolitis)* is often considered to be an allergic phenomenon The connection between sarcoidosis and allergy has frequently been mentioned

Intermittent hydrarthrosis arthritis and rheumatic fever are considered by some workers to be manifestations of allergy

A study of the list of diseases produced by drugs (p 286) is perhaps the best way for the physician to acquaint himself with the great variety of reactions and diseases which have been proved to occur in persons hypersensitive to ordinary innocuous agents

Progress of knowledge in these important fields of medicine depends largely on the body of unequivocal evidence which can be adduced For this reason and for the sake of the individual patient critique and objectivity are imperative in every case The physician must be careful not to classify as allergic any miscellaneous clinical condition until he is able to demonstrate at will, by skin test clinical test or other means the presence and the effect of the specific eliciting allergen whether it be inhalant, food drug therapeutic serum product of micro organisms or other agent

SPECIFIC MANAGEMENT

In all the miscellaneous allergies the available immunologic approaches consist in attempts to avoid or to reduce exposures to the suspected allergens

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